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EDITORIAL

Metabolic surgery: A paradigm shift in type 2 diabetes management

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Abstract

Obesity and type 2 diabetes mellitus (T2DM) are major public health issues globally over the past few decades. Despite dietary interventions, lifestyle modifications and the availability of several pharmaceutical agents, management of T2DM with obesity is a major challenge to clinicians. Metabolic surgery is emerging as a promising treatment option for the management of T2DM in the obese population in recent years. Several observational studies and a few randomised controlled trials have shown clear benefits of various bariatric procedures in obese individuals in terms of improvement or remission of T2DM and multiple other health benefits such as improvement of hypertension, obstructive sleep apnoea, osteoarthritis and non-alcoholic fatty liver disease. Uncertainties about the long-term implications of metabolic surgery such as relapse of T2DM after initial remission, nutritional and psychosocial complications and the optimal body mass index for different ethnic groups exist. The article discusses the major paradigm shift in recent years in the management of T2DM after the introduction of metabolic surgery.

Key words: Metabolic surgery; Bariatric procedures; Type 2 diabetes mellitus; Body mass index; Diabetes remission

Core tip: Metabolic surgery or bariatric surgery has revolutionised the 21st century management of type 2 diabetes mellitus (T2DM) in obese patients. Marked reduction of body weight following the bariatric procedures results in improvement or remission of T2DM in a significant number of patients along with improvement of other diseases associated with obesity

such as hypertension, obstructive sleep apnoea, osteoarthritis and non-alcoholic fatty liver disease. Uncertainty exists about the long-term outcomes in terms of diabetes relapse, nutritional and psychosocial complications. However, the marked benefits of metabolic surgery outweigh the risks related to the procedure that has resulted in a major paradigm shift in the management of obese population with T2DM in recent years which is the topic of discussion of this paper.

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METABOLIC SURGERY: A PARADIGM SHIFT IN TYPE 2 DIABETES MANAGEMENT

Obesity has become a global pandemic in recent years that affects more than 600 million adults worldwide[1]. World Health Organization estimated that 39% of adults aged 18 years and over were overweight [body mass index (BMI) $\geqslant$ 25 kg/m^2; more than 1.8 billion persons], and 13% were obese (BMI $\geqslant$ 30 kg/m^2) in the year 2014. A majority of these individuals reside in the developed countries although obesity and overweight are major public health issues even in developing nations. The National Health and Nutrition Examination Survey 2011-2012 regarding population prevalence in obesity revealed that 34.9% of the adults were obese and 33.6% were overweight in the United States[2]. Although data on the prevalence of obesity is scant from most other countries, comparable figures probably exist in many developed countries.

Obesity is a major risk factor for type 2 diabetes mellitus (T2DM). By 2014 diabetes affected 387 million people worldwide and 4.9 million deaths in 2014 alone were directly related to diabetes[3]. The global diabetes disease burden is mainly from T2DM and a majority of these cases are related to obesity. Despite diet and lifestyle interventions and the availability of pharmaceutical agents with weight losing properties the long-term management of obesity with these measures are disappointing. Different gastric bypass procedures collectively termed as bariatric surgery/metabolic surgery have emerged as very promising methods to treat obesity in the past 3 decades that can improve and potentially cure diabetes and many other diseases related to obesity. Through this paper we discuss the major paradigm shift in the management of T2DM in recent years after the introduction of metabolic surgery. We also discuss the long-term health benefits, adverse complications and emerging research questions related to metabolic surgery.

TYPES AND EFFICACY OF DIFFERENT BARIATRIC PROCEDURES

Although there are a multitude of bariatric procedures developed over the past 50 years the common techniques used in present day clinical practice are adjustable gastric banding (AGB), sleeve gastrectomy (SG), Roux-en-Y gastric bypass (RYGB) and bilio-pancreatic diversion (BPD). The different surgical procedures are depicted in the Figure 1.

AGB and SG are predominantly restrictive procedures whereas RYGB and BPD are mainly mal-absorptive procedures that reduce effective area of nutrient absorption in the intestinal mucosa. Food passes through the alimentary limb in RYGB and BPD with gastrointestinal secretions in the bilio-pancreatic limb mixing with the nutrients where both limbs form the common channel.

In various randomised controlled trials (RCTs), the reported mean percentage (%) excess body weight loss (with 95%CI in parenthesis) achieved at one year after AGB, SG and RYGB were 33.39 (22.57-44.21), 69.70 (41.09-98.32) and 72.32 (64.60-80.04) respectively[4]. The % excess weight loss (%EWL) reported with BPD was 76.89 ± 1.53 that is significantly higher than RYGB (67.17 ± 1.43; P = 0.0004)[5]. AGB procedures are losing popularity in the recent years because of inferior efficacy and the necessity for repeated surgery in a higher proportion of cases years after the initial surgery[6]. Although BPD is associated with a significantly higher %EWL and T2DM remission compared to other bariatric procedures the post-operative complication rates are higher[7] making this a less preferred operation.

BARIATRIC SURGERY IN T2DM

The major RCTs reporting the effects of metabolic surgery on T2DM are summarised in Table 1. The total number of patients in these RCTs is relatively small for a common condition like T2DM and the duration of follow-up is limited to 12-24 mo. However there are cohort studies and non-randomized trials reporting benefits of metabolic surgery from different regions of the world. There are also a few systematic reviews and meta-analyses reporting the beneficial effects of bariatric procedures in T2DM.

In a meta-analysis of weight loss and remission of T2DM evaluated in RCTs and observational studies (OBS) of bariatric surgery *vs* conventional medical therapy over a 17 mo period the mean excess weight loss (EWL) for the bariatric surgery and the conventional treatment groups were 75.3% and 11.3% respectively; the corresponding T2DM remission rates were 63.5% and 15.6%[12]. The limitation of the meta-analysis was that many short-term OBS were included and surgery was not always compared directly to more vigorous medical weight loss interventions. There was lack of

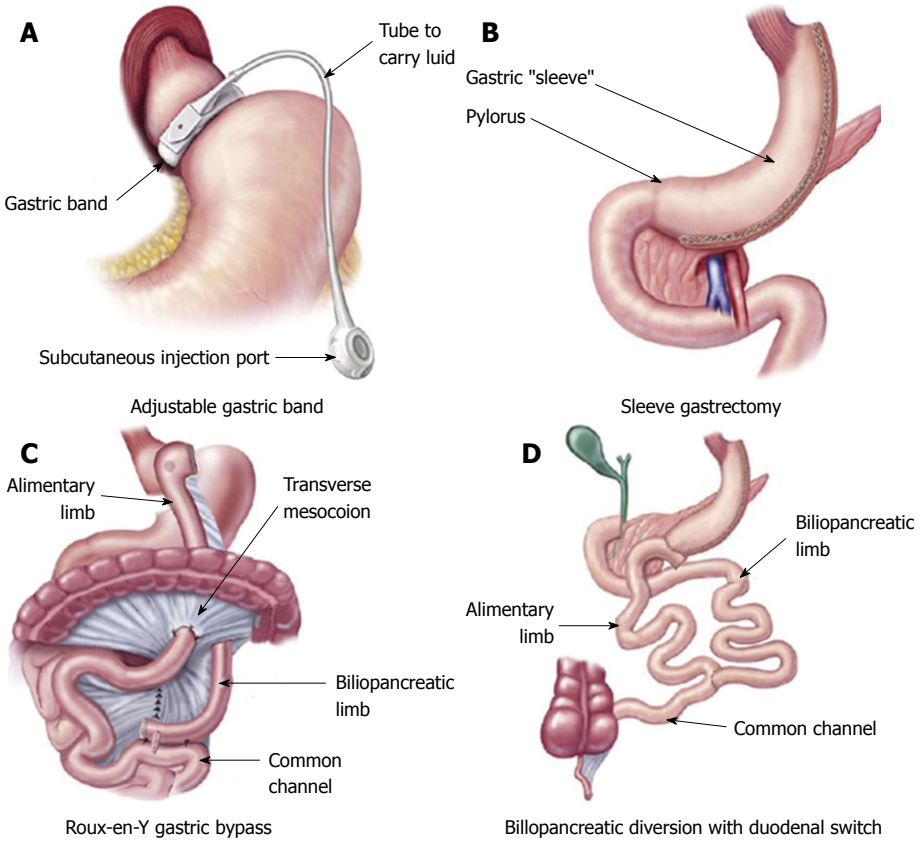

Figure 1 The diagrammatic representation of different bariatric surgical procedures. A: Adjustable gastric band; B: Sleeve gastrectomy; C: Roux-en-Y gastric bypass; D: Bilio-pancreatic diversion. Figure reproduced with permission from John Wiley and Sons. *Obesity* (Silver Spring) 2013 Mar; **21** Suppl 1: S1-27.

standardization in the definition of diabetes remission and it was unclear how specific bariatric procedures were chosen or what criteria were used for performing bariatric surgery.

A comparison of the mean changes in BMI and haemoglobin A1c (HbA1c) achieved with individual procedures[12] are shown in the Table 2.

A few long-term cohort studies give us insight on the beneficial effects of metabolic surgery in T2DM[16]. For example, the Swedish Obese Subjects (SOS) study, started in 1987 is a prospective case-control study with 2010 obese subjects who underwent bariatric procedures (predominantly vertical banded gastrostomy which is considered to be less effective and no longer undertaken)[16,17]. A 72% remission of T2DM after two years and 36% durable remission after 10 years were observed in obese subjects in the SOS study[16,18]. Compared to control the risk of developing T2DM was reduced by 96%, 84%, and 78% after 2, 10, and 15 years in obese subjects without T2DM at baseline[19].

Utah obesity study retrospectively compared 7925 obese subjects who underwent RYGB with the same number of age, sex and weight matched controls and after an average follow up period of 7.1 years, found a 40% reduction in all cause mortality, 49% reduction of mortality from cardiovascular diseases and 92% reduction of death related to T2DM[20]. The Longitudinal Assessment of Bariatric Surgery (LABS-2) study is an ongoing multi-center cohort study that showed T2DM remission in 67% and 28% of those who underwent RYGB and AGB respectively after 3 years of follow up[21].

MECHANISMS OF DIABETES IMPROVEMENT/REMISSION FOLLOWING METABOLIC SURGERY

Reduction in calorie intake

Typically, patients are put on a calorie-restricted diet after bariatric procedures. The average caloric intake ranges from 400-800 kcal/d in the first month[22]. Calorie restriction has a significant impact on hyperglycemia with reduction of blood glucose levels. In fact, in a recent case-control study[23], post-bariatric diet implemented before metabolic surgery resulted in more profound glucose reduction in T2DM patients than in the post-surgical period, indicating the role of calorie restriction in glycemic control after bariatric procedures. Very low calorie diet alone resulted in improvement of insulin sensitivity and β-cell function in obese T2DM cases (comparable to those who had bariatric surgery) in the short-term[24]. Generally, a calorie-restricted diet should be maintained in patients following metabolic surgery on a long-term basis.

Table 1 Major randomised controlled trials reporting effects of metabolic surgical procedure on type 2 diabetes mellitus

RCT	Study details	Outcome	Diabetes remission
Dixon *et al*[8]	Un-blinded RCT. *N* = 60 Obese patients with recent onset T2DM Conventional therapy *vs* LAGB Follow-up: 2 yr	Weight loss –1.7% ± 5.2% in conventional group and –20.7% ± 8.6% in the surgical group	73% in surgical group 13% in conventional group (Remission of T2DM defined as FBS < 7.0 mmol/L and HbA1c < 6.2%)
Mingrone *et al*[7]	Single centre non-blinded RCT. *N* = 60. Severely obese patients. T2DM of at least 5 yr duration and HbA1c > 7.0%. Conventional medical therapy *vs* RYGB or BPD Follow-up: 2 yr	Weight loss −4.7% ± 6.3% with medical therapy, −33.3% ± 7.8% with RYGB and −33.8% ± 10.1% with BPD	75% in RYGB group; 95% in BPD group. None in the conventional group (Remission defined as FBS < 5.6 mmol/L and HbA1c < 6.5%)
Schauer *et al*[9]	Single centre non-blinded RCT in obese uncontrolled T2DM. *N* = 150 Intensive medical therapy *vs* RYGB or SG Follow-up: 12 mo	Weight loss –5.4 ± 8.0 kg in medical therapy group, -29.4 ± 9.0 kg in RYGB group and –25.1 ± 8.5 kg in SG group	12% medical therapy group 42% in RYGB group 37% SG group (Remission/primary outcome defined as HbA1c of 6% or less)
Ikramuddin *et al*[10]	Un-blinded RCT in obese T2DM with HbA1c over 8% with average duration of 9 yr. *N* = 120 Intensive medical therapy *vs* RYGB Follow-up: 12 mo	Difference in weight loss between surgical and medical group –17.1 ± 5.6 kg. % weight change in medical *vs* Surgical group –7.9 ± 2 *vs* –26 ± 2	75% RYGB group 32% in medical group (Remission defined as HbA1c < 7%)
Liang *et al*[11]	RCT in obese T2DM. *N* = 108. RYGB compared with standard care with or without Exenatide therapy Follow-up: 12 mo	Reduction in BMI (kg/m^2) in standard *vs* Exenatide *vs* RYGB: –0.56 ± 1.66 *vs* –3.44 ± 1.21 *vs* –5.97 ± 0.91	90% in RYGB group None in patients receiving standard care with or without Exenatide (Remission defined as HbA1c < 6.5%)

RCTs: Randomised controlled trials; T2DM: Type 2 diabetes mellitus; *N*: Number of subjects; LAGB: Laparoscopic gastric banding; FBS: Fasting blood sugar; RYGB: Roux-en-Y gastric bypass; SG: Sleeve gastrectomy; BPD: Bilio-pancreatic diversion.

Table 2 The mean changes in body mass index and haemoglobin A1c achieved with different gastric bypass procedures

Bariatric procedure	Body mass index (kg/m^2)			HbA1c (%)		
	Pre-surgery	Post-surgery	Mean reduction (95%CI)	Pre-surgery	Post-surgery	Mean reduction (95%CI)
AGB	37	29.5	7.5 (5.9-9.1)	7.8	6	1.8 (1.3-2.3)
SG	41.3	28.3	13.0 (10.1-15.9)	7.9	6	1.9 (1.0-2.8)
RYGB	34.6	25.8	8.8 (5.2-12.4)	8.2	6.1	2.1 (1.3-2.9)
BPD	50.5	34.6	15.9 (11.8-20.0)	8	5.2	2.8 (2.1-3.5)

AGB: Adjustable gastric banding; SG: Sleeve gastrectomy; RYGB: Roux-en-Y gastric bypass; BPD: Bilio-pancreatic diversion; HbA1c: Haemoglobin A1c.

Alterations in gut hormones

The acceleration of gastrointestinal transit time after bariatric procedures results in augmented secretion of gut hormones such as glucagon-like peptide-1 (GLP-1), Glucose-dependent insulinotropic peptide (GIP) peptide-YY (PYY) and oxyntomodulin (OXM) that alter energy and glucose metabolism[25]. The anorexient and weight losing properties of GLP-1 is well established in experimental and clinical models. Several studies showed significant elevation of GLP-1 levels during oral glucose challenge and with meals after bariatric procedures such as SG[26], RYGB[27] and BPD[28]. Elevated GLP-1 levels following metabolic surgery was also shown to reverse the obesity-induced endothelial dysfunction conferring cardiovascular protection in the obese[29].

Increased PYY levels following bariatric procedures result in weight loss in obese subjects. PYY administration resulted in a 30% reduction in the calorific value of a meal consumed 2 h after PYY infusion and a 33% reduction in food consumption over 24 h period in human beings[30]. Similarly, OXM administration has been shown to reduce appetite, amount of food ingested and body weight[31]. Ghrelin (a gut-derived peptide hormone that stimulates hunger) level was found to be low after RYGB, whereas the level was high in diet-induced weight loss, indicating the impact of suppression of hunger signals in subjects following bariatric surgery[32]. Hypergastrinemia following SG has been recently reported in rat models of T2DM, although its impact on metabolic pathways and body weight changes have been unclear[33]. The alteration in these gastrointestinal hormonal factors together contributes to significant improvement in T2DM and the body weight of the individual.

Pancreatic β-cell function

Improvement in insulin sensitivity and pancreatic β-cell function are important factors that contribute to improvement/remission of T2DM in obese subjects. Increase in secretion of incretin hormones (GLP-1 and GIP) and proliferation of the β-cell mass have been demonstrated following bariatric procedures in human beings and experimental animals[34]. Although these

factors clearly contribute to T2DM control, there may be other mechanisms which are not yet clear.

Hepatic and peripheral insulin sensitivity

Significant improvement of hepatic insulin sensitivity is observed within few days of bariatric procedures much earlier and before significant weight loss occurs. Reduction of energy intake from the post-bariatric diet may contribute significantly to the improvement in hepatic insulin sensitivity. Although peripheral insulin sensitivity is not altered in the immediate post-operative period, delayed improvement is observed in patients[25,35]. Reduced hepatic fat content and body weight loss account for the sustained improvements in hepatic and peripheral insulin sensitivity during long-term follow up of patients who had metabolic surgery[25].

Role of bile acids

Bariatric procedures were shown to increase the plasma levels of bile acids that improved glucose and lipid metabolism[25,36]. However, the exact mechanisms by which bile acids improve glycemic control and body weight remain elusive.

Gut microbiata

Major changes in the gut microbiota have been demonstrated following bariatric procedures in animal models and human beings[37]. Increase in numbers of some of these intestinal microbial flora, and the related changes in the gut biochemical environment, may affect glucose and lipid metabolism that contribute to weight loss and diabetes improvement[25,37]. More research is necessary on the role of gut flora in glucose and fat metabolism following bariatric procedures.

Body weight loss and diabetes remission

The major mechanism by which improvement and/or remission of T2DM occurs in obese subjects following metabolic surgery is the significant weight loss after the procedure. Analysis of participants in the Look AHEAD (Action For Health in Diabetes) study clearly showed a progressive increase in odds ratios for HbA1c reduction with higher proportions of weight loss[38]. The odds ratios for % weight reduction (in parenthesis) were: 1.80 ($\geqslant$ 2 to < 5), 3.52 ($\geqslant$ 5 to < 10), 5.44 ($\geqslant$ 10 to < 15) and 10.02 ($\geqslant$ 15%) respectively for HbA1c reduction of 0.05% in the study subjects. Substantial loss of body weight post-bariatric surgery therefore would explain the remarkable improvements in glycemic control and even remission of T2DM in the majority of patients.

Overall, a multitude of physiological, behavioural and anatomical alterations following the bariatric procedure result in significant improvements in metabolic and glycemic parameters that may even result in potential cure of T2DM in a good number of patients after the metabolic surgery.

COST BENEFITS AND OTHER HEALTH-RELATED OUTCOMES

Data from the National Bariatric Surgery Registry (NBSR) of the United Kingdom that included 18283 cases from 2010 to 2013 clearly showed compelling evidence of the cost effectiveness of bariatric surgery as a treatment option for severely obese T2DM patients[39]. NBSR data showed that 61% of patients with obstructive sleep apnoea could come off their treatment after surgery 65% of patients with T2DM could stop their diabetic medications. A recent systematic review and meta-analysis revealed important cardioprotective effects of metabolic surgery in terms of regression of left ventricular hypertrophy, improvement of diastolic function and reduction of left atrial size[40]. Improvement of hypertension, hypercholesterolemia, gastro-esophageal reflux disease, and arthritis are some of the other reported major beneficial effects of bariatric surgery[41].

IMMEDIATE AND LONG-TERM COMPLICATIONS

The main complications in the immediate post-operative period are pulmonary complications, vomiting, wound infections, bleeding and anastomotic leak[16,17]. In a recent systematic review and meta-analysis the peri-operative and post-operative mortality rates were 0.08% and 0.31% respectively in RCTs and 0.22% and 0.35% respectively in OBS[4]. The overall complication rates were 17% in RCTs and 10% in OBS, and the reoperation rates were 7% and 6% respectively.

The most common long-term complications were iron deficiency anaemia in up to 15% of cases and re-operations in up to 8%[14,16]. Psychological issues are emerging as an important complication on follow up of the cases, and alcohol overconsumption and substance misuse are increasingly being reported in patients on long-term follow up[16,42]. For unknown reasons, the suicidal rates were found to be higher in patients who underwent bariatric surgery[16,20]. Nutritional deficiencies including deficiencies of calcium, vitamin D, iron, zinc, and copper, are common after bariatric surgery[16,43]. Periodic checking for deficiencies and nutritional supplements are indicated in patients.

Massive weight loss after the surgery may result in abnormal body contour because of extensive skin folds that may affect the psychological well being of many patients. Body contouring surgery improves this problem and may help improvement of physical and mental well being in these patients although financial cost may become an issue in many healthcare systems[44]. Post-prandial hypoglycaemia is a common problem in many patients after metabolic surgery. Rapid transit of contents from stomach with smaller capacity could be a reason in many cases that can be treated with small frequent

meals and complex carbohydrates. However, severe hypoglycaemic episodes caused by hyperinsulinemia from pancreatic islet cell hyperplasia (nesidioblastosis) can sometimes be crippling necessitating pancreas resection, reversal of gastric bypass and restriction of gastric pouch in extreme cases[45].

Diabetic microvascular complications such as retinopathy, neuropathy and nephropathy can sometimes get worse if there is rapid (abrupt) improvement of longstanding severe dysglycemia in patients with poorly controlled diabetes. A similar situation could be expected following metabolic surgery with acute improvement in glycaemic control. There is some evidence of worsening of pre-existing diabetic retinopathy in a proportion of cases following bariatric procedures, although improvement of the disease is also noted in some others[46,47]. Therefore, counselling about this potential complication before surgery and close monitoring after the procedure are advisable. Though the data is insufficient, there is some evidence for improvement of diabetic neuropathy[48] and nephropathy[49] after bariatric surgery. There are no reports of worsening of these conditions after improvement of T2DM following bariatric procedures.

Pregnancies after bariatric surgery were found to be associated with significantly lower risk of gestational diabetes [odds ratio (OR): 0.25; 95%CI: 0.13–0.47], large-for-gestational-age infants (OR: 0.33; 95%CI: 0.24-0.44) and shorter gestation (mean difference: −4.5 d; 95%CI: −2.9 to −6 d; $P < 0.001$)[50]. However, there were significantly higher risk of small-for gestational-age infants (OR: 2.20; 95%CI: 1.64-2.95; $P < 0.001$). The risk of stillbirth or neonatal death post-bariatric pregnancies appeared to be higher [1.7% *vs* 0.7% (OR: 2.39; 95%CI: 0.98-5.85; $P = 0.06$)] although this risk did not reach statistical significance.

APPROPRIATE PATIENT CATEGORY FOR METABOLIC SURGERY

There is no clear and uniform consensus from different international bodies about the minimum BMI cut off for consideration of the bariatric procedure in obese individuals. The National Institute for Health and Clinical Care Excellence (NICE) of the United Kingdom recently recommended bariatric surgery for people with a BMI of > 40 kg/m^2 and > 35 kg/m^2 in the presence of co-morbidities such as T2DM or hypertension[51]. For people of Asian family origin a lower BMI threshold should be considered. NICE also recommends expedited assessment for Bariatric surgery to people with BMI of 30-34.9 kg/m^2 who have recent onset T2DM. This is based on the evidence that earlier intervention can improve the chances of remission following bariatric surgery[39].

The Canadian Diabetes Association Clinical Practice Guidelines (2013) recommend bariatric surgery for people with class Ⅲ obesity (BMI $\geqslant$ 40.0 kg/m^2) or class Ⅱ obesity (BMI = 35.0 to 39.9 kg/m^2) in the presence of co-morbidities, with an inability to maintain weight loss following adequate trial of health behaviour intervention[52].

The American Association of Clinical Endocrinologists, the Obesity Society and the American Society for Metabolic and Bariatric Surgery (2013) recommend metabolic surgery in obese individuals with a BMI of $\geqslant$ 40 kg/m^2 without coexisting medical problems and surgical risk[53]. For patients with BMI $\geqslant$ 35 kg/m^2, surgery may be offered if one or more severe obesity-related co-morbidities exist including T2D, hypertension, hyperlipidemia, obstructive sleep apnea (OSA), obesity-hypoventilation syndrome (OHS), Pickwickian syndrome (a combination of OSA and OHS), nonalcoholic fatty liver disease or nonalcoholic steatohepatitis, pseudotumor cerebri, gastroesophageal reflux disease, asthma, venous stasis disease, severe urinary incontinence, debilitating arthritis, or considerably impaired quality of life. Patients with BMI of 30–34.9 kg/m^2 and T2DM or metabolic syndrome may also be offered a bariatric procedure, although evidence for this recommendation is inadequate with the unavailability of long-term data[53].

With robust clinical and epidemiological data emerging from all continents of the world, a global consensus on the appropriate patient categories that get definite benefits from metabolic surgery is expected to emerge in the near future.

AREAS OF UNCERTAINTY

Although there is accumulated experience from different regions of the world on the excellent outcomes of bariatric procedures, there is not enough data from resource poor nations of Asia, Arabian Peninsula, Africa and South America to generalise the recommendations of metabolic surgery, even though obesity epidemic is becoming a public health issue in these regions. Moreover, the BMI cut off for obesity in Asians is different from that of the western populations. For example BMI of $\geqslant$ 25 kg/m^2 is considered as obesity in India[54] and $\geqslant$ 27 kg/m^2 in Taiwan[55]. Diabesity (diabetes caused by overweight or obesity) is different for populations of Asian and Afro-Caribbean ethnic background owing to the difference in abdominal adiposity in these groups compared to other races, making generalisation of BMI cut offs metabolic surgery inappropriate.

For a common condition like diabetes there are only a handful of RCT's of short duration comparing bariatric surgery to medical therapy which ranged from standard care to intensive medical intervention. There are a few prospective studies available on long term outcomes of bariatric surgery. However, T2DM being a lifelong multisystem disease with almost all organs of the body involved, more data based on lifelong follow up of cases is necessary to understand the true impact of bariatric procedures. This requires maintenance of nationwide bariatric registries globally along the lines of NBSR in the UK which can provide valuable information.

Though there are some studies on the impact of bariatric surgery on the psychosocial, nutritional and

mineral metabolic status of patients, long-term data on these areas are still inadequate. Similarly the optimal management of post-bariatric nesidioblastosis that emerged as a challenging clinical problem is not yet clear.

Different multicentre on-going prospective clinical trials would be expected to answer these unresolved questions.

CONCLUSION

Metabolic surgery is emerging as a major paradigm shift in the 21st Century management of T2DM, and has revolutionised the care of diabesity. Massive weight loss with remission of T2DM in a significant proportion of cases along with improvement of most other obesity-related ailments makes the treatment a very attractive option for clinicians and patients. A recent analysis of the NBSR data clearly showed its cost effectiveness. Appropriate patient selection and long-term follow up of cases are necessary to optimise the outcomes and reduce the complications.

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EDITORIAL

Impact of new technologies on diabetes care

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Abstract

Technologies for diabetes management, such as continuous subcutaneous insulin infusion (CSII) and continuous glucose monitoring (CGM) systems, have improved remarkably over the last decades. These developments are impacting the capacity to achieve recommended hemoglobin A1c levels and assisting in preventing the development and progression of micro- and macro vascular complications. While improvements in metabolic control and decreases in risk of severe and moderate hypoglycemia have been described with use of these technologies, large epidemiological international studies show that many patients are still unable to meet their glycemic goals, even when these technologies are used. This editorial will review the impact of technology on glycemic control, hypoglycemia and quality of life in children and youth with type 1 diabetes. Technologies reviewed include CSII, CGM systems and sensor-augmented insulin pumps. In addition, the usefulness of advanced functions such as bolus profiles, bolus calculators and threshold-suspend features will be also discussed. Moreover, the current editorial will explore the challenges of using these technologies. Indeed, despite the evidence currently available of the potential benefits of using advanced technologies in diabetes management, many patients still report barriers to using them. Finally this article will highlight the importance of future studies tailored toward overcome these barriers to optimizing glycemic control and avoiding severe hypoglycemia.

Key words: Diabetes; Technology; Glycemic control; Quality of life; Outcomes; Management

Core tip: There have been many advances in the technologies associated with diabetes care in the last few years, which have resulted in new opportunities

in the treatment of diabetes. Despite the encouraging results and the prospect of a fully automated closed loop system in the near future, metabolic control remains suboptimal in most patients with type 1 diabetes. Data from registries has recently shown that a large proportion of children with type 1 diabetes does not meet the age associated A1c targets across all countries, especially in the youth age. This editorial discusses the impact of these technologies on glycemic control and quality of life and attempts to address how to overcome barriers using these technologies to achieve improved metabolic control.

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Recently, data related to the safety and effectiveness of a bionic pancreas under unrestricted outpatient conditions were published by Russel *et al*[1], reporting that "as compared with an insulin pump, a wearable, automated, bi-hormonal, bionic pancreas improved mean glycemic levels, with less frequent hypoglycemic episodes" in both adults and adolescents with type 1 diabetes, in outpatient settings. While the device is still imperfect, (difficulty with wireless connectivity, poor stability of glucagon, need for faster insulin analogues, risk of hypoglycemia and need for restrictions in food and alcohol intake) these results marked an important step toward a fully automated closed-loop system.

Currently, at least 20 research groups are working worldwide on glucose-sensor-controlled automated insulin delivery systems (closed loop pumps), and during the last years, great progress was reported in closed-loop system in outpatients settings, with a particular focus on overnight glycemic control, whereas postprandial and post-exercise glucose control remains a challenge[2-5].

These promising studies bring the artificial pancreas closer to public use, which is possible due to the recent improvements in technology for diabetes care. Nonetheless, many patients spend the majority of their day outside the recommended glycemic ranges. As a result glycemic control remains suboptimal for many patients with type 1 diabetes[6].

It has now been 10 years since the Epidemiology of Diabetes Interventions and Complications study confirmed the need to optimize glycemic control as early as possible to sustain risk reduction for micro- and macro vascular complications[7,8]. Since then, many national and international diabetes associations [*e.g.*, the American Diabetes Association and the International Society for Pediatric and Adolescent Diabetes (ISPAD)] revised their guidelines for type 1 diabetes management and now recommend a target glycated hemoglobin (A1c) of 6.5%-7.5% (48-59 mmol/mol) for most people with type 1 diabetes (T1D)[9,10]. However, recently published data by McKnight *et al*[11], reported that only 30% of males and 29% of females aged < 15 years, 24% of males and 20% of females aged 15-24 years, and 30% of males and 28% of females aged > 25 years achieved these recommended A1c levels (< 7.5% or < 59 mmol/mol). These data confirmed that this target is not easily achieved in many people with type 1 diabetes and also that A1c levels are higher in those aged 15-24 years than among other age groups across many countries[11]. It is clear that there is still a gap between patients' glycemic control outcomes and what can be achieved with newer therapeutic improvements, even if technological key advances as the continuous subcutaneous insulin infusion (CSII) and the continuous glucose monitoring (CGM) have been shown to greatly improve diabetes care.

Focusing on the effectiveness of new technologies and the limitations of the use of such technologies in the real world may help find a way to achieve the A1c goals for many patients. In addition, it could give us greater insight into barriers to sustain the use of these therapeutic advances and how to overcome them. Several recently published review studies and meta-analyses addressed these topics[12-14]. Deeb *et al*[15] assessed the association between how insulin pumps were used and blood glucose control to determine if the use of advanced pump features improved glycemic control. Indeed, over the last 15 years, it has been shown that the increasing use of insulin pump can result in many health benefits and an improvement of overall treatment satisfaction[16,17]. Thus, it would be expected to improve long-time metabolic outcome in patients using this treatment. Although randomized controlled studies and systematic reviews of pediatric cohorts using CSII showed only modest benefits (in the range of 0%-0.9%[18]) in terms of mean A1c compared to multiple daily injections (MDI), many prospective and retrospective case-control studies, clinic-based series and registries, reported that pediatric insulin pump users have a lower A1c when compared to patients using MDI, and that they are more likely to achieve A1c targets than those on injections. Recently, Olsen *et al*[19] showed a significantly lower mean A1c ($P < 0.0001$) in 1493 children and youth using CSII *vs* 1846 using MDI therapy over a 5 year period in all age groups. In the T1D Exchange clinic registry, A1c was shown to be lower in CSII users *vs* MDI users (7.9% *vs* 8.5%, $P < 0.001$); in the longitudinal analysis, one year after initiation of CSII therapy, A1c decreased by 0.2% on average ($P < 0.001$), with no difference in frequency of severe hypoglycemic events ($P = 0.2$)[20]. Similar data have been reported in the national pediatric diabetes audit of England and Wales and in the DPV initiative of Germany and Austria at the last ISPAD meeting[21]. What is more, in their meta-analysis, Pickup and Sutton reported patients on CSII had less hyperglycemia and less severe hypoglycemia[22]. Other meta-analyses showed that the frequency of severe hypoglycemia was significantly higher with multiple daily insulin injections

than with insulin-pump therapy [odds ratio (OR), OR: 4.19; 95%CI: 2.86-6.13). The greatest reduction was seen among patients who had had the greatest number of episodes of severe hypoglycemia while they were receiving injection therapy. Among these patients, the rate of severe hypoglycemia was higher by a factor of about 30 with multiple daily insulin injections than with insulin-pump therapy[16].

Finally, CSII has been associated with an improved quality of life[23,24]: CSII use is related to reduced frequency and intensity of parent stress, decreased fear of hypoglycemia, increased flexibility in quantity and timing of meals and sleep schedule, improvement in diabetes self-efficacy and independence[23,25].

However, not all children benefit from CSII. This discrepancy allows us to determine predictors for improvement of glycemic control on pump. For example, Olsen *et al*[19] showed that achievement of target A1c was significantly associated with lower A1c before insulin pump therapy initiation, younger age (< 12 years), shorter diabetes duration, higher number of daily boluses and more frequent daily self-blood glucose monitoring. Thus, patient characteristics are critical factors in deciding whether or not it is appropriate to prescribe an insulin pump to an individual.

Similar results are seen with continuous glucose monitors (CGM) use, and data from the T1D Exchange Clinic Registry showed that only a small proportion of patients with type 1 diabetes are using CGM daily in clinical practice, especially in the pediatric age range[26]. The accuracy and usability of CGM has gradually improved over the past decade so that the overall accuracy of the latest sensor generations measured as the mean relative absolute difference *vs* a given laboratory standard is in the 8%-15% range[27]. Despite this, CGM is still far from perfect. For example, more accurate evaluation of interstitial glucose levels during hypoglycemic events are necessary as CGM performs poorly in the hypoglycemic range, and the lag time between interstitial glucose and blood glucose, increased sensor sensitivity and inappropriate calibration require improvement[28].

Several studies have showed that CGM is associated with a significant reduction in A1c[29]. In two recent meta-analyses of randomized controlled trials, CGM was shown to be superior to self-monitoring of blood glucose alone in reducing A1c by almost 0.4% in both children and adults[30,31]. In a JDRF-sponsored multicenter trial, there was a larger percentage of subjects 8-14 years old using CGM who achieved at least a 10% decrease in A1c and a target A1c < 7% (59 mmol/mol), compared with children using capillary blood monitoring (SMBG)[32]. In a Cochrane meta-analysis, the largest improvement in glycemic control was observed in poorly controlled diabetes patients using CGM and CSII (sensor-augmented pump - SAP). There was no increase in risk of severe hypoglycemia or ketoacidosis in this evaluation.

Although the impact of CGM use on hypoglycemia is less clear, Floyd *et al*[31] found a significant decrease in the duration of time in both mild and severe hypoglycemia ranges and an increase in the time "in range" (70-180 mg/dL) in patient using CGM[31].

In the last few years, several studies evaluated the impact of SAP on metabolic control compared to either MDI or SMBG[33] or CSII and SMBG[34-36]. SAP therapy was demonstrated to be effective at lowering mean A1c in both adult and pediatric patients[33-36]. Switching to SAP therapy helped patients using MDI to lower their A1c levels to the same extent as the patients originally allocated to the SAP arm of the study. Benefits persisted through the entire 12-mo study phase (STAR 3 Study)[33], as well as its follow up phase[34]. Patients using SAP therapy were more likely to meet age-appropriate A1c target[33].

However, studies investigating the effectiveness of SAP in patients already using the insulin pump showed conflicting results, ranging from no significant benefit to significantly improved glycemic control[35-37].

SAP therapy was also associated with decreased time spent in hypoglycemia compared to MDI or CSII, but few significant results were found in the rate of severe hypoglycemic events.

Although current standards for diabetes management reflect the need to avoid diabetes complications, in the pediatric clinical setting, the fear of hypoglycemic events is a common barrier to achieving optimal metabolic control.

It has been reported that the most severe hypoglycemic events in children occur at night, and account for 75% of all hypoglycemic seizures[38]. Thus, children may represent a group of patients that can benefit greatly from SAP therapy, especially when a low-glucose suspend (LGS) feature is implemented (*i.e.*, the feature that automatically suspends insulin delivery when the blood glucose is less than a pre-selected value, typically 70 mg/dL). LGS and predictive low-glucose suspend (PLGS) are the first steps toward the artificial pancreas, and can help reduce family stress related to glucose management, especially overnight. LGS systems have been demonstrated to be effective in reducing the rate, severity and duration of hypoglycemia, without an increase in A1c[39]. In particular, this feature was shown to be most effective in patients with more frequent and severe hypoglycemia and in those with hypoglycemia unawareness[39].

In a study from Ly *et al*[40] the incidence of hypoglycemia after 6 mo decreased from 34.2/100 patient-months in the insulin pump group to 9.5/100 patient-months in the SAP plus LGS group, with the rate of severe hypoglycemia reduced to zero (0) in the SAP plus LGS group[39,40].

In the PLGS system, a predictive algorithm stops insulin delivery prior to reaching a predetermined threshold. Only a few outpatients studies using PLGS have been published to date, but it was shown that a further reduction of the severity of hypoglycemia as compared with SAP plus LGS alone is possible[41,42].

Despite all these encouraging results, CGM use is still difficult in youth with type 1 diabetes of all ages[43]. It is

now clear that CGM can greatly help to improve glycemic control only in patients with type 1 diabetes who use the sensor for the majority of time (more than 70%)[29,31,32], and works best when used on a near-daily basis. For this reason, physical, socioeconomic and educational factors that could impact the use of this technology are an area of current research, as are predictors of pump and sensor use[44].

There are a number of barriers that may inhibit youth from wearing CGM. CGM use requires significant patient input (sensor insertion, calibration, response to sensor alarms and glucose trends) and ongoing SMBG for insulin dosing. The Juvenile Diabetes Research Foundation CGM trial on CGM satisfaction reported pain in sensor insertion, frustration with sensor alarms, skin reaction, and issues related to discomfort with wearing the device or technical problems as barriers to CGM wear[44]. In the T1D Exchange registry, CGM use was more likely in subjects with higher educational level, higher income, private insurance, longer diabetes duration and those on insulin pump[26]. In addition, recent data showed that most patients using CGM may not receive the full benefits of this technology, either because they do not use it enough or because they do not regularly download it and retrospectively review the data from the device[45].

Lack of a proper education, diminished motivation, deliberate insulin omission, and behavioral attitude can affect patients' compliance. Ensuring long-term follow-up with intensifying education and involving behavioral therapy in training might improve adherence and enhance treatment satisfaction, leading to a better glycemic control[26].

Beside technology by itself, great improvement has been observed also in immune-suppressor drugs or other drugs, useful to improve type 1 diabetes management[46].

In conclusion, since most of the recently reported epidemiological data demonstrates that a large proportion of type 1 diabetes patients do not achieve A1c targets, we consider increased education on diabetes care as a good option to improve glycemic control. New technologies may have positive outcomes, but can underperform if the technology is not used as expected[16,42-45].

While the hope for a fully automated artificial pancreas available in the near future remains, it is crucial to develop approaches for implementing and sustaining the use of technological advances that are currently available (*e.g.*, beside CSII and CGM). In addition, we need to continue our patient/family education efforts.

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EDITORIAL

Importance of telemedicine in diabetes care: Relationships between family physicians and ophthalmologists

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Abstract

Diabetic retinopathy (DR) is the worldwide leading cause of legal blindness. In 2010, 1.9% of diabetes mellitus (DM) patients were legally blind and 10.2% had visual impairment. The control of DM parameters (glycemia, arterial tension and lipids) is the gold standard for preventing DR complications, although, unfortunately, DR still appeared in a 25% to 35% of patients. The stages of severe vision threading DR, include proliferative DR (6.96%) and diabetic macular edema (6.81%). This review aims to update our knowledge on DR screening using telemedicine, the different techniques, the problems, and the inclusion of different professionals such as family physicians in care programs.

Key words: Diabetic retinopathy; Telemedicine; Family physicians; Clinical decisions support system; Diabetic retinopathy screening

Core tip: If telemedicine is especially suited for a particular medical specialisation, that specialisation is undoubtedly ophthalmology. The enormous healthcare pressure derived from the general population's high demand for vision control and the prevalence of certain diseases which affect the eyes, such as diabetes mellitus, combined with the tremendous progress in diagnostic imaging systems in this speciality make it especially possible to send images over telemedicine networks for the diagnosis or even prevention of eye diseases, thus making the demand for the use of these types of methods extremely important.

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INTRODUCTION

If telemedicine is especially suited for a particular medical specialization it would undoubtedly be ophthalmology. There is enormous pressure on healthcare systems by the general population's high demand for vision control and the prevalence of certain diseases which affect the eyes, such as diabetes mellitus (DM). The tremendous progress in diagnostic imaging systems make it possible to send images over telemedicine networks for the diagnosis or even prevention of eye diseases.

We should not forget that eye-care centers are often a considerable distance away from the population that require healthcare, so being able to send information over a telemedicine network is a great advantage. Good liaison among specialists, such as the ophthalmologist and the family doctor, means that it is possible to avoid patients traveling and enabling them to be diagnosed and controlled closer to home.

In spite of ophthalmology perhaps being the best example of the use of telemedicine, the reality is that its use is still far from extensive. There are many problems that ophthalmologists and other specialists who could use this communication system may face, including incompatibility among data-processing systems used by different specialists, not only among specialists and general practitioners, but even among hospital centers themselves. This is heightened by the existence of personal data-protection laws that cover the sending of images along with other personal details of patients. All this can make the regular use of telemedicine quite difficult[1].

Even within the field of ophthalmology, not all eye diseases can benefit from the use of telemedicine, the most common being to send images of diseases that affect the retina, many of them highly prevalent.

TELEMEDICINE IN DIABETIC RETINOPATHY

DM is recognized by the World Health Organization as an genuine pandemic[2] that affects more than 10% of the population over 14 years of age[3], with type diabetes mellitus 2 (DM2) being the most common presentation and associated with lifestyle habits such as sedentarism or obesity. Considered a chronic disease, its morbidity is brought about by the complications it causes throughout a patient's lifetime, these being mainly derived from damage to large vessels, or macroangiopathy (complicated by cerebrovascular accidents and myocardial infarction), or damage to small vessels, or microangiopathy, leading to nephropathy, neuropathy or retinopathy.

Eye diseases caused by microangiopathy or diabetic retinopathy (DR) are the main cause of blindness among young adults in the western world (aged between 45 and 60) and are closely related to poor metabolic control of the DM and aggravated by other comorbidities that are present in DM, such as high blood pressure, dyslipidemia or nephropathy. Early diagnosis of DR is very important because it has been shown that strict control over glycemia and high blood pressure slows the progress of the retinopathy and, if it is not present, extends the time until its appearance[4]. Screening diabetics is therefore fundamental for detecting the existence of DR as soon as possible. This should be carried out by taking retinal photographs with non-mydriatic cameras, an accepted cost-effective method that makes it feasible to cover a large number of patients with DM[5,6].

In spite of the fact that a system such as the one presented here would enable the screening of a large number of patients, with the benefit for the diabetic population this represents, the truth is that, to date, the screening of diabetic patients does not take place on a general basis and many patients with DM do not undergo regular eye examinations. So much so that in developed countries such as those in the European Union area, there are considerable deficiencies in compliance with eye examinations for diabetic patients.

With this in mind, the European "Screening for DR in Europe" group revised the 1990 St Vincent Declaration[7]. A large group of ophthalmologists and endocrinologists from 29 European countries attended a number of meetings between 2005 and 2011, which revealed a series of difficulties in applying screening recommendations. Such difficulties were identified as a paucity of information supplied to the public regarding screening visits, a shortage of teams and training programs, and insufficient collaboration among general practitioners, endocrinologists and ophthalmologists. In view of this data, it was decided to implement systematic screening programs designed to reach at least 80% of diabetics by using staff and professionals specially trained for this purpose.

When deciding to implement a system of DR screening, we need to consider what type of healthcare professional should be responsible for controlling patients with DM. In the majority of countries this is the family doctor, with control by endocrinologists being restricted to patients with very poor metabolic control of the DM.

The family doctor was, therefore, the professional who it was thought should be able to ensure collaboration with DR screening, even though there was some reticence among some sectors, especially ophthalmologists and optometrists. The insufficient number of ophthalmologists for such large populations such as diabetics, combined with different studies on the effectiveness of screening by general practitioners[8-10], led the different working groups to decide that the family doctor needs to be involved in the DR screening programs provided they are

experts in the analysis of retinal photographs and have the support of an ophthalmologist who can supervise them, without this implying non-performance of complete eye examinations[11] . In the United Kingdom, a country where screening has been more widely developed, general practitioners are included in the programs and different professionals are involved in assessment (general practitioners or optometrists)[2,12]. Furthermore, in the authors' healthcare areas, the general practitioner plays an important role in DR screening[13,14]. It is therefore essential to impart the necessary training to these professionals so that they can detect the presence of an incipient retinopathy and establish contact with reference ophthalmologists[14,15] so that the latter can then provide the required support. If more advanced forms of retinopathy are detected, they would be able to refer the patient for treatment as quickly as possible.

Telemedicine is clearly of great use to this system of DR screening making it possible to send images and information for a correct diagnosis, and disturbing diabetic patients as little as possible.

In the authors' experience, including general practitioners and ensuring they are appropriately supervised by ophthalmologists who are experts in DR, has enabled the screening of a large number of diabetics[16,17]. Since 2007, from an estimated population of 17792 diabetics, it has been possible to screen 15396 patients (86.53%), with 3.18 ± 1 visits during these 7 years. The scheme involves firstly training general practitioners, who would then be responsible for analyzing the retinal photographs of diabetics in their area. In the event of any suspicion of the presence of signs suggesting DR, the reference ophthalmologist would be consulted, and he/she then makes the final diagnosis and decides how to manage the patient. This procedure has led to the detection of an annual incidence of between 8.06% and 8.92% of patients with DR, with the incidence of patients with diabetic macular edema being between 2% and 2.8% per year. It is also important to note that between 9.2% and 10.3% of other pathologies have been detected each year, including macular degeneration associated with age, pathological myopia and the presence of pigmented lesions such as nevi. In spite of the efforts we have made in our area, only between 32.40% and 41.16% of diabetic patients undergo screening for DR every year. Part of the problem is that screening is opportunistic rather than systematic, and poor awareness among the population.

With the current world economic crisis and the explosion of the prevalence of DM we are witnessing, we should strive to ensure that screening programs are more sustainable. Measures that should be considered include: (1) Extending screening intervals for patients who do not apparently have DR and have good metabolic control (biannual is sufficient). This has been studied by some groups and proven to be feasible; (2) Developing a diagnosis aid system by implementing the design of clinical decisions support system software to enable risk factors to be considered when scheduling successive screening tests; and (3) Automatic reading of retinal photographs. Considerable advances have been made in this field, although these systems are currently very sensitive but not specific.

CONCLUSION

Telemedicine is a field that is extremely useful in ophthalmology and which has enormous potential, even though it is currently under-used and often limited to merely transmitting images and information about very specific pathologies such as DR or retinopathy in premature babies but has potential for many more eye diseases. Problems in data-processing systems can be solved and do not need to be an obstacle, but the lack of government regulation in many countries makes it difficult to apply in the vast majority of cases. Guidelines for government regulation are essential if communication among professionals is to increase, which can only lead to improving public health.

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REVIEW

Respiratory failure in diabetic ketoacidosis

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Abstract

Respiratory failure complicating the course of diabetic ketoacidosis (DKA) is a source of increased morbidity and mortality. Detection of respiratory failure in DKA requires focused clinical monitoring, careful interpretation of arterial blood gases, and investigation for conditions that can affect adversely the respiration. Conditions that compromise respiratory function caused by DKA can be detected at presentation but are usually more prevalent during treatment. These conditions include deficits of potassium, magnesium and phosphate and hydrostatic or non-hydrostatic pulmonary edema. Conditions not caused by DKA that can worsen respiratory function under the added stress of DKA include infections of the respiratory system, pre-existing respiratory or neuromuscular disease and miscellaneous other conditions. Prompt recognition and management of the conditions that can lead to respiratory failure in DKA may prevent respiratory failure and improve mortality from DKA.

Key words: Diabetic ketoacidosis; Respiratory failure; Hypokalemia; Hypomagnesemia; Hypophosphatemia; Pulmonary edema; Adult respiratory distress syndrome; Pneumonia; Neuromuscular disease

Core tip: Despite progress in its management, diabetic ketoacidosis (DKA) continues to cause significant morbidity and mortality. One of the conditions aggravating the course of DKA and causing several deaths is respiratory failure, which can be detected at presentation or, more frequently during the course of treatment of DKA. Several risk factors for respiratory failure in DKA are preventable. Early recognition and management of these risk factors, as well as early recognition of respiratory failure have the potential to improve both morbidity and mortality resulting from DKA.

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INTRODUCTION

Ketoacidosis in subjects with type 1, or less frequently, type 2 diabetes mellitus remains a potentially life-threatening diabetic manifestation. The subject has justifiably attracted attention in the literature. Sequential reviews[1-9] have documented important changes in the clinical concepts that are related to diabetic ketoacidosis (DKA) and its management. A large number of case series of DKA have addressed various aspects of its clinical presentation and management. For this review, we selected representative studies focused on management, outcome, age differences, gender differences, associated morbid conditions, ethnicity and prominent clinical and laboratory features[10-35].

In recognition of the complexity of treatment, the recommendation to provide this care in intensive care units was made more than 50 years ago[36]. Severe DKA is treated in intensive care units today[31]. Evidence-based guidelines for the diagnosis and management of DKA have been published and frequently revised in North America[37,38] and Europe[39]. Losses of fluids and electrolytes, which are important causes of morbidity and mortality in DKA, vary greatly between patients. Quantitative methods estimating individual losses and guiding their replacement have also been reported[40,41].

The outcomes of DKA have improved with new methods of insulin administration[42] and adherence to guidelines[43-46]. The aim of treatment is to minimize mortality and prevent sequelae. One study documented that the target of zero mortality is feasible[42]. However, mortality from DKA, although reduced progressively in the early decades after the employment of insulin treatment[1], remains high. Up to fifty plus years ago, mortality from DKA was between 3% and 10%[1,16]. A recent review reported a death rate from hyperglycemic crises of 7.5% in the United States, with greater mortality from hyperglycemic hyperosmolar state (HHS) than from DKA[9]. Reported mortality from DKA varies among age groups and countries. In various academic medical centers, death rate from DKA was < 1%[26,27] and < 2% among adult patients younger than 65 years[24] in the United States, 0.4% in Japanese children without and 4.7% with coma[23], 6.5% in adult Mexican patients[25], 4.1% in adult Israeli patients[34] without differences between men and women[29], 5.8% in adult Thai patients[30], 3.6% in adult Nigerian patients[32], around 13% in Indian children[33,47], and 22% in American patients older than 65 years[24]. In an autopsy study, DKA was identified as a major cause of death in diabetic patients[48].

One general observation impacting the outcome of DKA is that its management is not always optimal. Several reports documented varying degrees of non-adherence to guidelines[49-51], despite their proven effectiveness. The last of these reports also documented an increasing prevalence of DKA[51]. In addition to adherence to guidelines, efforts to reduce mortality from DKA should focus on individual causes of death. Causes of death in DKA were analyzed in several studies[23,25,27,30-34,52-55]. Cerebral edema and sepsis were the two most common causes. In a study from Greece reporting a 12.9% death rate, multivariate analysis identified the following as predictors of mortality from DKA: co-morbidities, severe acidemia at presentation (arterial blood pH < 7.0), high dose of insulin and persistence of hyperglycemia, and the development of coma or fever during treatment[54]. Another study from Indonesia reporting 40% death rate identified coma plus high serum lactate levels (> 4 mmol/L) as poor prognostic factors[55].

In this review, we analyzed the causes, mechanisms, management and prevention of respiratory failure which is one of the causes of death in DKA. Respiratory or cardiorespiratory deaths were reported in several series of DKA[25,27,31,34,47]. Respiratory failure may either be recognized at presentation or, more frequently, develop during the course of treatment of DKA. The main purpose of the review is to underline the diagnosis, pathogenesis, management and, in particular, prevention of respiratory failure in DKA through proper management.

DIAGNOSIS OF RESPIRATORY FAILURE IN DKA

The key features establishing the diagnosis of DKA are the presence of metabolic acidosis and large amounts of ketones (acetone, acetoacetic acid, beta-hydroxyburyric acid) in serum and urine. Hyperglycemia may be absent in some patients complicating the diagnosis of DKA[56]. DKA should be differentiated from other conditions producing increased ketone formation including alcoholic ketoacidosis and starvation ketosis. Lactic acidosis from sepsis or hypovolemia is another type of metabolic acidosis which occurs frequently during the course of

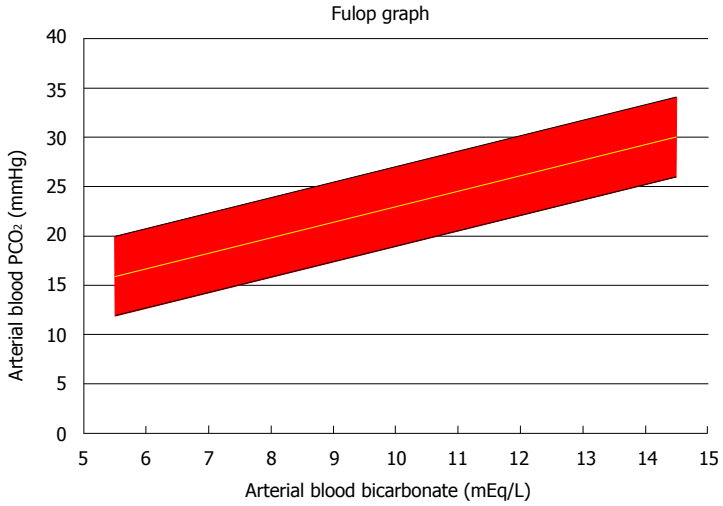

Figure 1 Arterial PCO_2 response to serum bicarbonate concentration in diabetic ketoacidosis. The draft, which was drawn using Fulop's regression equation[60], shows the mean and 95%CI of this response.

both DKA and HHS that should be differentiated from DKA. Serum lactate level should be measured in all patients with hyperglycemia and metabolic acidosis.

Assessment of the severity of DKA is primarily based on the degree of the acid-base disturbance. The most recent version of the United States guidelines for hyperglycemic crises in adults[38] set three levels of DKA severity: mild, moderate and severe. Criteria common to all three categories included plasma glucose > 250 mg/dL, positive serum and urine ketone test, and variable levels of effective serum osmolality, calculated as [2 × (serum sodium) + (serum glucose.mg/dL)/18]. The criteria that differed between the three categories were arterial blood pH (mild: 7.25-7.30, moderate: 7.00 to < 7.25, severe: < 7.00), plasma bicarbonate ([HCO_3]p, mild: 15-18 mEq/L, moderate: 10 to < 15 mEq/L, severe: < 10 mEq/L), serum anion gap calculated as [serum sodium − (serum chloride + serum bicarbonate)] (mild: > 10 mEq/L, moderate: > 12 mEq/L, severe: > 12 mEq/L) and mental status (mild: alert, moderate: alert/drowsy, severe: stupor/coma). The European guidelines for DKA in children[39] classify the severity of DKA only by the magnitude of metabolic acidosis (mild: venous pH < 7.30, [HCO_3]p: < 15 mEq/L. Moderate: pH < 7.20, [HCO_3]p: 10 mEq/L. Severe: pH < 7.10, [HCO_3]p: < 5 mEq/L).

In addition to its use in the diagnosis of DKA and establishing its severity, blood gas analysis provides two objective criteria for assessing the presence and severity of respiratory failure complicating DKA. The universal feature of respiratory failure is hypoxemia. Arterial blood PO_2 (PaO_2) at room air should be evaluated in all patients presenting with DKA. The second parameter of arterial blood gases that allows detection of respiratory failure in DKA is the arterial PCO_2 ($PaCO_2$). The application of $PaCO_2$ in the detection of respiratory failure complicating DKA merits some discussion.

It has been known for a long time that there is a predictable alveolar ventilatory compensation, within narrow limits, to a given degree of metabolic acidosis[57-59]. In its simplest form, this compensation is expressed as $PaCO_2$ as a function of [HCO_3]p. The ventilatory response to metabolic acidosis was analyzed by Fulop[60] in a series of 27 episodes of DKA uncomplicated by lactic acidosis or other acid-base disturbances. Fulop derived the following regression equation, which is almost identical to the original Winters equation[57] that was derived from several types of metabolic acidosis: $PaCO_2$, mmHg = 7.27 + 1.57 × ([HCO_3]p, mEq/L])

Figure 1 shows the 95% confidence area defined by Fulop's study. Fulop's diagram should be used to evaluate every case of DKA. This diagram may assist in the detection of associated other primary acid-base disorders, for example metabolic alkalosis from vomiting[61]. In addition, its use is critical for the detection of respiratory abnormalities accompanying the DKA. Fulop's diagram allows detection of an associated primary respiratory alkalosis. In this instance, the measured $PaCO_2$ is below the corresponding low 95% confidence limit in the Fulop diagram. Primary respiratory alkalosis is not rare in DKA[62,63]. Detection of primary respiratory alkalosis in a patient with DKA has great importance because it often provides a clue for the presence of sepsis[62] which is the underlying cause of DKA in many instances[37-39], respiratory distress secondary to cerebral edema, and other causes of respiratory alkalosis.

The second critical use of Fulop's diagram is in the detection of respiratory failure complicating DKA. In this case the $PaCO_2$ value is higher than the corresponding upper limit for $PaCO_2$ in the Fulop diagram. Such a finding should lead to a systematic search for potential causes of respiratory failure and frequent monitoring of the respiratory status of the patient including arterial blood gases.

Detection of respiratory failure in DKA is not based only on PaO_2 and $PaCO_2$ values. A diligent search for coexisting conditions adversely affecting the respiratory function has also great importance. Respiratory failure is

Table 1 Risk factors for respiratory failure in diabetic ketoacidosis

Depletion of primarily intracellular ions
Potassium
Magnesium
Phosphate
Pulmonary edema
Hydrostatic (cardiogenic)
Non-hydrostatic (adult respiratory distress syndrome)
Respiratory tract infections
Pneumonia
Infections of the airways
Miscellaneous conditions
Neuromuscular disease
Non-infectious diseases of the respiratory tract
Other

more often encountered during treatment of DKA than at its presentation, as will be shown later. Consequently, vigilance for any clinical or laboratory clue suggesting development of respiratory failure should be maintained throughout the treatment of DKA.

One potential pitfall of Fulop's equation is that it may not compute the respiratory response to profound degrees of DKA with accuracy. Soubani *et al*[64] suggested that there are limits for hyperventilation resulting from metabolic acidosis or sepsis. Subsequently, Guh *et al*[65] derived different regression equations of $PaCO_2$ on $[HCO_3]p$ in DKA patients with arterial pH > 7.10 ($PaCO_2 = 6.6 + 1.65 \times [HCO_3]p$) and those with arterial pH ⩽ 7.10 ($PaCO_2 = 2.88 + 3.18 \times [HCO_3]p$). The regression equation for DKA with moderate acidemia was similar to Fulop's equation. The Guh equation for severe acidemia appears to differ from Fulop's equation. Indeed, there are substantial differences between the two equations for $[HCO_3]p$ values that are not extremely low. For example, for $[HCO_3]p$ equal to 10 mEq/L, Fulop's equation calculates an appropriate $PaCO_2$ of 23 mmHg (95%CI: 23-27 mmHg). From the Henderson-Hasselbach equation, the resulting arterial pH value is 7.24 (95%CI: 7.19-7.34). The corresponding values obtained from the Guh equation for severe acidemia are $PaCO_2$ 34.0 (95%CI: 30.6-37.4) mmHg, and arterial pH 7.09 (95%CI: 7.05-7.14). However, the differences between the two equations are trivial in cases of profound acidosis. For example, we used the same equations to calculate the ventilatory responses and arterial pH values for $[HCO_3]p$ equal to 3 mEq/L: from Fulop's equation, the values were $PaCO_2$ 12.0 (95%CI: 8-16) mmHg; arterial pH 7.02 (95%CI: 6.89-7.19); from Guh's equation, the values were $PaCO_2$ 12.4 (96%CI: 9.0-15.8) mmHg; arterial pH 7.01 (95%CI: 6.90-7.14). We suggest that Fulop's diagram is appropriate for evaluating the alveolar ventilation in profound DKA. In addition, vigilance for other clues of potential respiratory failure (hypoxemia, history of pulmonary or neuromuscular disease, clinical monitoring of the respiratory system) should be enhanced in this instance.

Metabolic acid-base parameters (pH, plasma bicarbonate concentration) were found to be comparable between venous and arterial blood samples in uncomplicated cases of DKA[66-68]. However, venous blood gas determination is not appropriate for the detection of respiratory failure in the course of DKA[66] for two reasons: The first reason is that venous blood measurements cannot detect abnormalities in the partial pressure of oxygen caused by ventilatory failure, especially in states of hypotension and tissue hypoperfusion. The second reason is that the regression equations used for detection of inadequate ventilatory response to DKA were developed in arterial blood. Transcutaneous monitoring of carbon dioxide has been proposed as a means of monitoring the treatment of DKA[69]. Determining the accuracy of this technique in identifying respiratory failure in DKA will require further research.

The diagnosis of respiratory failure during the course of DKA can be greatly facilitated by a systematic search for risk factors that have been identified to specifically complicate the course of DKA. Clinicians should also be alert for pre-existing respiratory insufficiency and for conditions that can cause respiratory failure independently of DKA (*e.g.,* severe hypothyroidism). The next section addresses risk factors for respiratory insufficiency associated with DKA. Detailed discussion of all causes of respiratory failure is beyond the scope of this review.

RISK FACTORS FOR RESPIRATORY FAILURE IN DKA

Table 1 shows these factors. The first two categories listed in this table (depletion of primarily intracellular ions and development of pulmonary edema) are direct consequences of hyperglycemia and DKA. The last two categories (infections of the respiratory tract and miscellaneous risk factors) include conditions that may lead to DKA but are not caused by it.

Deficits of ions with primary intracellular distribution in DKA

Potassium, magnesium and phosphate are ions with primary intracellular distribution that are depleted as a consequence of DKA. Depletion of these ions has severe, but preventable, clinical consequences. Clinical manifestations relevant to this report are muscle weakness that can culminate in respiratory failure and cardiac dysrhythmias that may affect myocardial function. If appropriate replacement is not done, the depletion of these ions is more frequent and profound during treatment than at presentation with DKA[70]. A major aim of the treatment of DKA is to address the deficits of these ions. The mechanisms of deficit and their clinical consequences are discussed below. The mechanisms of potassium deficiency and of changes in serum potassium concentration in DKA will be discussed in some detail. Similar mechanisms create the abnormalities in the other two ions.

Potassium: There are disturbances in internal and external potassium balance in DKA. During development of DKA, the internal imbalance is caused by movement of potassium from the intracellular into the extracellular compartment causing hyperkalemia. The external imbalance is attributed to the fact that DKA causes losses of body potassium causing hypokalemia. The losses can be profound and are usually accentuated during treatment. In Martin's report[70], hyperkalemia was present in 39% of the DKA cases at presentation and in 4% of the cases after 12 h of treatment, while hypokalemia was present in 18% of the DKA cases at presentation and 63% of the cases after 12 h of treatment. The incidence of hypokalemia at presentation of DKA may be affected by factors independent of DKA, such as previous gastrointestinal loss of potassium or diuretic use[71]. In published reports of DKA, the frequency of hypokalemia at presentation varied between 0[17] and 36.7%[13]. A recent study found hypokalemia at presentation in 5% of patients with DKA[72].

Balance studies during development or treatment of DKA documented the abnormalities in external and internal potassium balance caused by DKA[73-79]. Potassium is lost in the urine during development of DKA because of osmotic diuresis caused by glycosuria. Urinary excretion of ketoacids oblicates the loss in the urine of equivalent amounts of cations, particularly sodium and potassium. The contribution of ketonuria to the urinary potassium loss has not been studied in DKA, to our knowledge. Nevertheless, the loss of potassium in DKA is often large. Patients with previously undiagnosed type 1 diabetes who present with DKA after protracted polyuria may have life threatening potassium deficits[41].

Despite the urine losses, large numbers of patients exhibit hyperkalemia at presentation with DKA[70,80,81], because of transfer of potassium from the intracellular into the extracellular compartment. The mechanisms of this transfer have been studied extensively. The most important underlying mechanism is absence of insulin action, which has direct and indirect effects on internal potassium balance. Directly, inhibition of basal insulin secretion causes loss of intracellular potassium[82] and hyperkalemia. Insulin causes hyperpolarization of the cell membranes and potassium entry into the cytoplasm[83] through an increase in the sites of the alpha-2 subunit of the sodium-potassium ATPase of the cell membranes[84]. The effect of insulin on cellular potassium uptake is dissociated from that on cellular glucose uptake[85].

Indirectly, absence of insulin action causes hypertonicity (elevated serum effective osmolarity) through both extracellular accumulation of solute (glucose) and osmotic diuresis, which causes loss of water in excess of monovalent cations[41]. Hypertonicity leads to transfer of water and intracellular solutes, particularly potassium, into the extracellular compartment[86]. Hyperkalemia will result in this case even if the state of hypertonicity has no effect on the transport mechanisms of cell membranes for potassium or on the electrical potential difference across the cell membrane[87]. Contraction of the extracellular volume as a result of osmotic diuresis tends to concentrate extracellular solutes including potassium and constitutes another source of hyperkalemia in DKA[41].

The hyperkalemic effects of the disrupted internal potassium balance described so far are encountered in DKA and all other hyperglycemic syndromes. The question whether metabolic acidosis has additional hyperkalemic effects in DKA has been a matter of controversy[88-90]. Two lines of research provide support for an added hyperkalemic effect of acidosis in DKA: Multivariate analysis in clinical studies identified arterial pH as a predictor of serum potassium level, in addition to serum glucose[91,92]. The other line of evidence is the recent discovery that acidosis affects potassium distribution across cell membranes though alterations in cellular membrane transporters[93].

For patients on maintenance dialysis, the hyperglycemic effects on internal potassium balance are almost completely unopposed because of absent or minimal osmotic diuresis. Studies of hyperglycemic syndromes in this group have provided support for an additional hyperkalemic effect of DKA when serum glucose concentration and effective osmolarity are comparable between DKA and HHS[94-99]. Finally, we are unaware of studies showing that the catabolic state induced by acidosis causes the release of cellular potassium into the extracellular compartment and contributes to the hyperkalemia. Nevertheless, there is sufficient evidence to support the concept of an independent hyperkalemic effect of DKA that is added to the other hyperkalemic effects of hyperglycemia. This further complicates the evaluation of potassium deficits in DKA.

Treatment of DKA leads to substantial declines in serum potassium concentration, even when large amounts of potassium are infused[100-107]. Multiple mechanisms contribute to the hypokalemic effect of treatment. These include a direct effect of insulin on cellular potassium uptake[83], correction of the hyperglycemic hypertonicity[96], dilution of extracellular potassium due to infusion of large volumes of fluids and continuing losses of potassium through the urine or the gastrointestinal tract.

Urinary potassium losses during treatment of DKA merit attention because they often do not constitute a treatment focus as they should. Urinary losses of potassium in DKA are accentuated by coexistent states of hyperaldosteronism[108]. Insulin has an effect similar to aldosterone on renal transport mechanisms of sodium and potassium and its administration to patients with DKA causes excessive renal potassium losses[109]. The other mechanism of excessive potassium losses during treatment of DKA is ongoing osmotic diuresis while serum glucose remains elevated[41]. Improvement of the renal circulation as fluid deficits are corrected has the potential of worsening potassium losses through osmotic diuresis.

Clinical consequences of hypokalemia associated with DKA were reported first in 1946 in a seminal paper

by Holler[110] who observed a patient who developed hypokalemia and respiratory failure during treatment of DKA and whose respiratory failure resolved after infusion of potassium salts. The significance of Holler's report was stressed in a more recent report[111]. Subsequently, a series of articles reported severe clinical manifestations secondary to hypokalemia developing or worsening during treatment of DKA[112-135]. The majority of the reported cases exhibited varying degree of respiratory failure. In several patients, respiratory failure was associated with severe cardiac manifestations and/or profound and generalized muscle weakness. Death occurred in some cases[122,129].

The management of DKA should adhere to guidelines that recommend the administration of intravenous potassium salts to patients presenting with DKA and hypokalemia and initiation of insulin infusion only after serum potassium has reached values > 3.3 mEq/L[38]. Serum potassium concentration should be monitored during treatment in all patients with DKA. In DKA patients presenting with hypotension, extreme hyperglycemia and hypokalemia, urine volume and urine potassium concentration should also be monitored during treatment in order to guide, along with serum potassium, changes in the rate of infusion of potassium salts[41]. Measuring potassium levels with the apparatus used for blood gas determination is not appropriate because these levels may vary substantially from simultaneous serum potassium determinations[136]. Finally, electrocardiographic changes may indicate changes in serum potassium during the course of DKA[137,138]. Monitoring of electrocardiogram to prevent inappropriate administration of potassium salts to patients with DKA has been proposed[137]. However, dissociation of plasma potassium concentration and electrocardiographic abnormalities in a patient on DKA has been reported[139]. Monitoring of serum potassium during the course of treatment of DKA should be primarily based on frequent determinations of serum potassium concentration. Electrocardiographic monitoring should be used as a guide for management of life-threatening hyperkalemia and for timely detection of dysrhythmias complicating the treatment of DKA.

Magnesium: In DKA body magnesium deficits through urinary losses are routinely encountered and are the consequence of absence of insulin[140]. However, magnesium exit from the cells may cause hypermagnesemia, which is frequent at presentation with DKA. The magnesium defect is unmasked during treatment. In Martin's study[70], hypomagnesemia was recorded in 7% of the cases at presentation with DKA and 55% of the cases after 12 h of treatment, while hypermagnesemia was found in 68% of the cases at presentation and 21% of the cases after 12 h of treatment.

In one reported case, profound hypomagnesemia caused respiratory failure and asystole, and cardiac function recovered after cardiopulmonary resuscitation and infusion of a large bolus of magnesium salts[141]. A small number of patients with DKA and severe hypomagnesemia were subsequently reported[142-144]. The development of hypomagnesemia during treatment of DKA was linked to infusion of potassium phosphate[142,144]. Aldosterone promotes urinary magnesium losses[145]. Magnesium loss in the urine during treatment of DKA may be increased because of the state of secondary hyperaldosteronism discussed in the subsection on potassium.

An important consequence of magnesium deficiency is that it causes excessive urinary losses of potassium and phosphate[146]. It is difficult to replete potassium stores when there are large magnesium deficits[147]. In addition to its direct and indirect effects on respiration, magnesium deficits have major effects on both cardiac contractility and rhythm. Insulin, along with its effects on cellular uptake of potassium and nutrients, increases intracellular free magnesium concentration in myocardial cells[148].

Magnesium deficit should be anticipated in patients with DKA. Serum magnesium concentration should be measured at presentation with DKA and should be monitored during treatment. Magnesium replacement should be guided by serum magnesium levels in this state.

Phosphate: Changes induced by DKA on both external and internal phosphate balances are similar to those of the balances of potassium and magnesium. Hyperglycemic osmotic diuresis causes urinary losses of phosphate, while metabolic acidosis causes shifts of phosphate from the intracellular into the extracellular compartment[149]. Insulin causes cellular phosphate uptake and a decrease in serum phosphate concentration[150,151]. The insulin-mediated decrease in serum phosphate concentration may be accentuated by dilution through intravenous replacement fluids and by continuing urinary losses. In Martin's study[70], hypophosphatemia was found in 11% of the cases at presentation with DKA and 71% of the cases after 12 h of treatment, while hyperphosphatemia was detected in 90% of the cases at presentation and was not detected after 12 h of treatment.

Severe hypophosphatemia has multiple adverse consequences[149]. Oxygen delivery to peripheral tissues is impaired by the depletion of red cell 2, 3 diphosphoglycerate (2,3-DPG), which causes a shift of the oxygen dissociation curve to the left thus impeding oxygen release. Depletion of high-energy phosphate compounds in muscles secondary to phosphate deficits causes muscle weakness and rhabdomyolysis, dysrhythmias, myocardial dysfunction and seizures[149,152,153].

A number of cases of development of severe hypophosphatemia with varying degrees of respiratory failure during the treatment of DKA have been reported[154-161]. Rhabdomyolysis was present in one patient[161]. A recent report found that the severity of metabolic acidosis at presentation affects the degree of hypophosphatemia during treatment of DKA[162]. Monitoring of serum phosphate should guide the replacement of phosphate deficit. Phosphate replacement was shown to be

effective in preventing the development of severe hypophosphatemia in this instance[163,164]. However, phosphate infusion has not been shown to improve the outcome of DKA in prospective studies[38] and may have adverse consequences including hypocalcemia and hypomagnesemia[142,143]. Phosphate should be replaced during treatment of DKA only if serum phosphate levels are low. The guidelines suggest rates of infusion of potassium phosphate and other ions[38]. The critical measure during treatment of DKA consists of close monitoring of the patient's clinical status and all serum components that are replaced[41].

Pulmonary edema secondary to DKA or its treatment

The second category of direct consequences of DKA is the development of pulmonary edema. Arterial blood gases are necessary for evaluation of its severity and to guide its treatment. Oxygen administration is guided by the degree of hypoxemia, which is universal in patients with pulmonary edema[165]. Abnormalities of $PaCO_2$ accompany the hypoxemia in the majority of the cases[166]. Respiratory alkalosis, triggered by the hypoxemia, is frequent in pulmonary edema. Eucapnia and respiratory acidosis are also present in substantial numbers of patients with acute pulmonary edema[165]. "Normal" or elevated values of $PaCO_2$ in patients with pulmonary edema indicate inadequate respiratory response to hypoxemia and should be considered as indicators of the severity of this condition. Elevated $PaCO_2$ levels have been reported in a small number of patients with end-stage renal disease and extreme hyperglycemia without DKA[63]. Two varieties of pulmonary edema in DKA have been are recognized, a hydrostatic form attributed to elevated pulmonary venous pressure and a form that develops because of increased pulmonary capillary permeability.

Hydrostatic pulmonary edema in DKA: Hydrostatic pulmonary edema is usually diagnosed at presentation with DKA or severe hyperglycemia without DKA and is corrected during the treatment of these syndromes. The sequence of pulmonary edema at presentation with severe hyperglycemia with or without DKA and its correction with insulin administration has been reported in patients with advanced renal failure[166-170]. Development of circulatory overload and hydrostatic pulmonary edema in these patients was initially attributed to the acute shift of a substantial volume of fluid from the intracellular into the extracellular compartment. This volume shift is an osmotic consequence of solute accumulation in the extracellular compartment during development of hyperglycemia. Correction of hyperglycemia with insulin administration shifts fluid back into cells[166].

The magnitude of osmotic translocation of fluid between the two major body fluid compartments that is secondary to hyperglycemia should affect the severity of the ensuing circulatory overload. This magnitude is affected by two main factors: The first and most obvious factor is degree of hyperglycemia. The volume of the osmotic fluid transfer increases as the serum glucose level increases in the same episode of hyperglycemia. The second factor affecting the volume of fluid transferred from the intracellular into the extracellular compartment during development of hyperglycemia is the baseline status of the extracellular volume. For the same degree of hyperglycemia, patients with preexisting peripheral edema develop larger osmotic fluid transfers than those without edema and the same baseline intracellular volume[171,172]. Insulin administration without any other therapeutic measures has led to correction of the pulmonary edema in the reported cases[166-170]. However, other measures, including mechanical ventilation and emergency ultrafiltration may be required in some patients.

The development of extracellular volume expansion may not be the only cause of hydrostatic pulmonary edema in DKA. This syndrome has been reported in DKA patients without advanced renal failure, who usually have volume deficits at presentation[173,174]. This suggests that the development of DKA may be due to factors other than extracellular volume expansion in some cases. In one instance, DKA was diagnosed during treatment of high altitude pulmonary edema[173]. Recovery required treatment of both conditions. It is not clear which condition appeared first.

In another case, hydrostatic pulmonary edema developed during treatment of DKA in a 9-year-old child[175]. Serum troponin levels were elevated and echocardiography showed segmental myocardial dysfunction when pulmonary edema was diagnosed. Repeated cardiac echocardiography was normal 6 d later. This case report illustrates the potential of DKA to cause acutely myocardial dysfunction. This dysfunction could be secondary to excessive fluid replacement. Another cause of myocardial dysfunction in DKA is absence of insulin. Insulin has inotropic effects in subjects with type 1 diabetes[175], subjects with type 2 diabetes[176] and normal controls[176]. It is unclear whether the resolution of pulmonary edema at presentation results from a correction of the extracellular volume excess or a direct action of insulin on myocardial contractility.

Non-hydrostatic pulmonary edema in DKA: Diabetes mellitus may affect the structure and function of the lungs, in addition to other target organs. Histological changes in the lungs of diabetic patients involve the wall of the alveoli and the pulmonary capillaries, while the most consistent functional changes include reduced lung volumes, reduced pulmonary elastic recoil, and reduced capillary lung volume leading to impaired diffusion capacity[177]. Respiratory function in these patients is apparently preserved under normal conditions, but their lung reserves are reduced and can cause clinical lung dysfunction under stressful conditions including volume overload[178]. The development of non-hydrostatic pulmonary edema [adult respiratory distress syndrome (ARDS)] in DKA may be related to the effects of stress on diabetic lungs.

Characteristically, ARDS is not present initially, but develops during the course of treatment of DKA. ARDS appears to be a more frequent and severe complication of DKA than hydrostatic pulmonary edema. A number of publications reported patients who developed ARDS during treatment of DKA[179-192]. ARDS developing during treatment of DKA may lead to death[192]. The severity of ARDS complicating the treatment of DKA is underlined by its association with cerebral edema.

DKA is one of the major causes of cerebral edema[193]. Cerebral edema usually develops during treatment of DKA[194] and is a major cause of mortality and long-term neurological sequelae[195]. Simultaneous development of cerebral edema and ARDS has been reported in several publications[28,196-203]. Research efforts have addressed factors that affect fluid transfers across blood capillary membranes of the brain and lungs during treatment of DKA. Early studies focused on Starling forces controlling fluid exchanges across capillary membranes. Infusion of large volumes of crystalloid solutions leads to increase in the capillary hydrostatic pressure and to dilution of serum proteins and decrease in the colloid osmotic pressure of the serum. Decreased serum colloid osmotic pressure was identified as a risk factor for ARDS during treatment of DKA[204-208].

Decreased serum colloid osmotic pressure may lead to increased fluid transfer from the intravascular into the interstitial space of various tissues including the lungs where it will cause respiratory distress. However, serum colloid osmotic pressure is not a key determinant of fluid transfers between interstitial fluid and intracellular compartment. Efforts to identify risk factors for the development of both ARDS and cerebral edema in DKA have been focused on altered capillary membrane permeability and changes in the serum effective osmolarity (tonicity). Increased pulmonary capillary permeability during treatment of ARDS was found in early reports[209,210]. The potential explanations include activation of lymphocytes[211] and release of cytokines, particularly interleukin-1 (IL-1)[212-215], the serum levels of which are much higher during treatment of DKA than at its presentation. These findings have linked the development of cerebral edema and ARDS in patients with DKA.

A potent driver of fluid exchanges between the extracellular and intracellular compartments is the tonicity of the extracellular compartment, which changes during treatment of DKA. Current strategy for preventing cerebral edema and ARDS consists of careful infusion of crystalloid solutions. Care should be exercised when selecting their volume and tonicity[41]. Replacement of volume deficits should be guided by the clinical picture: Deficits causing severe clinical manifestations should be replaced promptly with isotonic solutions. Monitoring of the clinical signs of hypovolemia (hypotension, tachycardia, low urine output) should guide the rate of infusion, which should be slowed down when these signs are corrected. Clinical monitoring is critical for adequate volume replacement and prevention of overshooting.

Hypertonicity is common in hyperglycemic syndromes and can be severe. Tonicity changes may play a role in the development of cerebral edema during treatment of DKA[203]. Tonicity changes have, in general, a substantially larger effect on intracellular volume than extracellular volume changes. Unlike volume deficits hypertonicity should be corrected slowly during treatment of DKA. The guidelines for management of hyperglycemic crises recommend an hourly decline in serum glucose concentration between 50 and 65 mg/dL[37], which corresponds to a decrease in serum effective osmolarity of between 1.2 and 2.8 mOsm/L[41]. An hourly rate of decrease in effective osmolarity $\leqslant$ 3 mOsm/L during treatment of DKA is desirable. Whether measures addressing lymphocyte function and cytokine production can be effective in preventing cerebral edema and ARDS during treatment of DKA are topics for future research.

Respiratory tract infections in DKA

Infections are known to be a major category of conditions precipitating DKA. A systematic search for infections is warranted in all patients presenting with DKA. This search is complicated by the similarity between symptoms of infection and those of DKA (malaise, abdominal distress, dyspnea, *etc*.) and by finding elevated white blood cell counts in both conditions. In addition, infections in the respiratory tract have the potential of causing respiratory failure in patients with DKA. Examples of respiratory tract infections reported to cause respiratory failure include pneumonia secondary to *Streptococcus pneumoniae*[134,216], *Legionella pneumonia*[217], *Klebsiella pneumonia*[218], *community-acquired pneumonia*[219], *influenza*[220], *pulmonary zygomycosis*[221], *mucormycosis*[222-225], *candidiasis*[224] and *coccidiomycosis*[226]. The list of respiratory tract infections that can cause respiratory failure during the course of DKA is, in all probability, much larger.

A complicating feature of DKA associated with lung infections is that severe volume deficits may mask the clinical and radiographic manifestations of pneumonia, which blossom after hydration[134]. This scenario represents one condition in which evaluation of the respiratory compensation to DKA in the arterial blood gases can offer an early sign of the presence of a condition complicating the DKA with the potential of respiratory failure[134].

Pneumonia associated with hyperglycemic symptoms is an independent predictor of short-term (28 d) mortality in both DKA and HHS[227]. Early diagnosis and management of pulmonary infections associated with DKA offers the promise of reducing this mortality.

Miscellaneous conditions associated with DKA

DKA may develop in patients with other serious medical conditions. Regardless of whether these conditions had an etiologic relationship with DKA or not, DKA aggravates their course. For example, development of respiratory stress from DKA during the course of conditions potentially causing respiratory failure, such as pre-

existing neuromuscular or pulmonary disease, should intensify the monitoring of the respiratory function.

Preexisting neuromuscular disease: DKA with respiratory failure has been reported in patients with Guillain-Barré syndrome[228,229] and one of the mitochondrial myopathies, the Kearns-Sayre syndrome[230]. Mitochondrial myopathies are associated with a high incidence of diabetes mellitus. Kearns-Sayre syndrome is characterized by progressive external ophthalmoplegia and cardiac conduction defects as its primary clinical manifestations. Patients with this syndrome exhibit multiple endocrine disorders including diabetes mellitus requiring insulin in about 15% of the cases[231]. This condition exemplifies the potential severity of DKA in the course of a neuromuscular disease. It is probable that patients with other types of mitochondrial syndromes causing myopathy develop DKA with respiratory failure. The reported case of DKA with respiratory failure in a patient with Kearns-Sayre syndrome had a fatal outcome[230].

Preexisting conditions of the respiratory system: We found reports of respiratory failure during the course of DKA in a patient with tracheal stenosis[232] and another patient with central venous catheter thrombosis[233]. DKA creates a severe stress on the respiratory function that has the potential to aggravate chronic lung disease. There is a paucity of studies addressing the effects of DKA on respiratory function in patients with chronic lung disease and on the outcomes of DKA in this setting.

Other associated conditions: The development of acute kidney injury during the course of DKA may place greater demands on respiratory function. Two reports addressed respiratory distress in patients with DKA and acute renal failure[234,235]. As previously noted, there is a great need for studies of DKA in patients with conditions potentially affecting the respiratory function (*e.g.*, drugs, severe hypothyroidism, *etc.*).

CONCLUSION

Respiratory failure developing during the course of DKA worsens its prognosis and is preventable in most instances. Prevention of respiratory failure has the potential to reduce mortality from DKA. Prevention and early detection of respiratory failure, by close monitoring of the clinical status and timely use and appropriate interpretation of arterial blood gases, have the potential of both decreasing mortality from DKA and preventing the debilitating somatic and psychiatric sequelae of prolonged mechanical ventilation[134].

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REVIEW

Gestational diabetes mellitus: Challenges for different ethnic groups

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Abstract

Ethnicity is defined as "belonging to a social group that has a common national or cultural tradition". Membership of certain ethnic groups has long been associated with increased risk of gestational diabetes mellitus (GDM). Studies that examined ethnic differences amongst women with GDM were often conducted in western countries where women from various ethnic backgrounds were represented. The prevalence of GDM appears to be particularly high among women from South Asia and South East Asia, compared to Caucasian, African-American and Hispanic communities. For some, but not all ethnic groups, the body mass index is a risk factor for the development of GDM. Even within a particular ethnic group, those who were born in their native countries have a different risk profile for GDM compared to those born in western countries. In terms of treatment, medical nutrition therapy (MNT) plays a key role in the management of GDM and the prescription of MNT should be culturally sensitive. Limited studies have shown that women who live in an English-speaking country but predominantly speak a language other than English, have lower rates of dietary understanding compared with their English speaking counterparts, and this may affect compliance to therapy. Insulin therapy also plays an important role and there appears to be variation as to the progression of women who progress to requiring insulin among different ethnicities. As for peri-natal outcomes, women from Pacific Islander countries have higher rates of macrosomia, while women from Chinese backgrounds had lower adverse pregnancy outcomes. From a maternal outcome point of view, pregnant women from Asia with GDM have a higher incidence of abnormal glucose tolerance test results post-partum and hence a higher risk of future development of type 2 diabetes mellitus. On the other hand, women from Hispanic or African-American backgrounds with GDM are more likely to develop hypertension post-partum. This review highlights the fact that management needs to be individualised and the clinician should be mindful of the impact that differences in ethnicity may have on the clinical characteristics and pregnancy outcomes in

women affected by GDM, particularly those living in Western countries. Understanding these differences is critical in the delivery of optimal antenatal care for women from diverse ethnic backgrounds.

Key words: Gestational diabetes mellitus; Ethnicity; Perinatal outcomes; Medical nutrition therapy; Prevalence

Core tip: The prevalence of gestational diabetes mellitus (GDM) is increasing world-wide, and studies have shown that optimal management of GDM improves pregnancy outcomes. This review summarises the differences in prevalence, clinical profile, management and pregnancy outcomes among women from various ethnic backgrounds who have GDM. Ethnicity is an important consideration in women affected by GDM, particularly in an antenatal service based in a Western society. There are particular challenges in individualising and tailoring medical nutritional therapy and insulin therapy. Also women from certain ethnic groups are at a higher risk of increased foetal and maternal morbidity and mortality. Understanding these challenges is important in providing optimal antenatal care for women of diverse ethnic backgrounds.

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INTRODUCTION

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first recognized during pregnancy[1]. GDM has been reported to affect between 1.4% to 12.3% of pregnancies[2], and its prevalence is increasing and parallels the rising incidence of type 2 diabetes mellitus worldwide[3,4]. Risk factors for developing GDM in pregnancy include obesity, previously GDM, glycosuria, family history, ethnicity and hypertension[5,6]. Arguably, one of the strongest non-modifiable risk factor for GDM relates to the woman's ethnicity.

The Oxford Dictionary defines ethnicity as "belonging to a social group that has a common national or cultural tradition"[7]. In particular, ethnic groups that are considered high-risk include Hispanic, African-Americans, Native American, South or South East Asian, Pacific Islander or Indigenous Australian[8]. It is also recognised that women with GDM from these and other ethnic groups may differ with regards to peri-natal and maternal outcomes[9-12].

In this review we discuss the differences amongst women from various ethnic groups in terms of prevalence, diagnosis, treatment of GDM and pregnancy outcomes. Because of the variance in the diagnosis and management of GDM around the world, it is difficult to compare women with GDM between countries. In order to delineate ethnic differences in terms of GDM prevalence, metabolic profiles of the women and pregnancy and long-term outcomes, studies were often conducted in the same country (or under the same health care system) where the diagnostic criteria, screening process, treatment regimen and delivery of health care are uniform for all women[13-16] (refer A Table 1).

DIAGNOSTIC CRITERIA

There are numerous diagnostic criteria for GDM currently being utilized in various parts of the world, as shown in Table 2. Many countries have based their GDM diagnostic criteria on the 1999 World Health Organisation (WHO) Criteria[17], while in Australasia and the United States, they have a adopted different glucose cut-offs to diagnose GDM based on the oral glucose tolerance test (OGTT)[18,19]. Findings from the Hyperglycaemia and Adverse Pregnancy Outcomes study has put impetus on revising the diagnostic criteria for GDM, and the International Association of Diabetes in Pregnancy Study Group (IADPSG) had subsequently recommended new threshold glucose levels on the 75 g OGTT for diagnosing GDM[20,21]. In 2013, the WHO adopted the IADPSG guidelines and revised the cut-offs for fasting plasma levels to $\geqslant$ 5.1 mmol/L, (92 mg/dL), 1-h glucose level to $\geqslant$ 10.0 mmol/L (180 mg/dL) and 2-h glucose level to $\geqslant$ 8.5 mmol/L (153 mg/dL) following 75 g OGTT[22]. It is expected that the 2013 WHO diagnostic criteria may standardise the diagnosis of GDM worldwide, but to date the implementation of this new criteria has been slow internationally.

There is preliminary data reflecting on the impact the new diagnostic criteria may have on the prevalence of GDM amongst different ethnic groups. A Singaporean study demonstrated that the proportion of women diagnosed with GDM in the Asian population using the 2013 WHO Criteria would be lower[23]. The prevalence could drop from 30.9% to 18.9% in women of Chinese ethnicity, and from 33.5% to 28.1% among the South Asian population[23]. On the other hand, in a predominantly Anglo-European population in Australia, the prevalence of GDM will increase from 9.6% to 13.0%[24]. The reason for this divergence is that there are differences between ethnic groups in the glycaemic profiles on the OGTT from which GDM is diagnosed. In a cohort of over 850 women diagnosed with GDM from a multi-cultural community in south western Sydney, Australia, from the 75 g OGTT, those from South-East Asia had the lowest fasting glucose levels (4.95 ± 0.65 mmol/L) but the highest 2-h glucose level (8.75 ± 1.17 mmol/L). In contrast, Pacific Islanders had the highest fasting levels (5.71 ± 1.19 mmol/L) but the lowest 2-h levels (7.73 ± 1.27 mmol/L)[25].

Table 1 Large studies highlighting the prevalence of gestational diabetes mellitus in women of different ethnicities living within a geographic region

Ref.	Year	City/region	Number of Women with GDM by ethnicity	Rate of GDM by ethnicity
Beischer *et al*[27]	1979-1998	Melbourne, Australia	66 Indian subcontinent	15% Indian subcontinent
			91 Chinese	13.9% Chinese
			60 Egypt and Arab countries	7.2% Egypt and Arab countries
			132 Other Asian	10.9% Other Asian
			95 Vietnamese	7.3% Vietnamese
			143 United Kingdom and Northern Europe	5.2% United Kingdom and Northern Europe
			270 Mediterranean	7.3% Mediterranean
			1008 Australian and New Zealand	4.3% Australian and New Zealand
Solomon *et al*[63]	1990-1994	The Nurses Health Study Ⅱ: 14 states in the United States	655 White	4.7% White
			12 African-American	10.6% African-American
			17 Hispanic	7.6% Hispanic
			26 Asian	10.5% Asian
Sullivan *et al*[64]	1997	Sydney, Australia	730 Vietnamese	5.3% Vietnamese
			7226 Australian	1.6% Australian
Savitz *et al*[28]	1995-2003	New York City, United States	398 North African	7.2% North African
			1018 Sub-Saharan Africa	5.9% Sub-Saharan Africa
			3512 East Asia	6.2% East Asia
			1027 South-East Asia and Pacific Islands	8.6% South-East Asia and Pacific Islands
			4758 South Central Asia	14.3% South Central Asia
			5038 Non-Hispanic Caribbean	6.8% Non-Hispanic Caribbean
			8767 Hispanic Caribbean	4.9% Hispanic Caribbean
			2780 Mexico	6.3% Mexico
			1133 Central American	4.9% Central American
			4189 South American	6.6% South American
			6387 African-American	34.3% African-American
			9846 Non-Hispanic White	3.6% Non-Hispanic White
Chu *et al*[29]	2005-2006	Up to 19 states in the United States	5326 Japanese	3.45% Japanese
			32460 Asian Indian	8.03% Asian Indian
			25530 Chinese	6.44% Chinese
			25785 Filipino	6.9% Filipino
			11561 South Korean	3.9% South Korean
			21721 Vietnamese	6.14% Vietnamese
			20718 Other Asian	5.07% Other Asian
			5761 Pacific Islander	5.17% Pacific Islander
			1873925 White non-Hispanic	3.82% White non-Hispanic
			394091 Black non- Hispanic	3.54% Black non- Hispanic
			677392 Hispanic	3.63% Hispanic
			14617 American Indian	5.13% American Indian
Kim *et al*[32]	2007-2009	California, United States	20129 Asian and Pacific Island	11.9% Asian and Pacific Island
			316 American Indian	7.6% American Indian
			3371 Black American	5.6% Black American
			52256 Hispanic	8.4% Hispanic
			1483 Other	6.6% Other
			18806 Non-Hispanic White	5.4% Non-Hispanic White

GDM: Gestational diabetes mellitus.

ETHNICITY AND THE PREVALENCE OF GDM

Specific ethnicities of women have long been considered as a risk factor for developing GDM. At-risk ethnic groups identified in the literature, are Aboriginal women in Australia, Middle Eastern (Lebanese, Syrian, Iranian, Iraqi or Afghanistan) women and Pacific Islanders[2,8,26,27]. Table 1 outlines some large population studies describing the prevalence of GDM among different ethnic groups who resided in western societies.

Among Asian women, the prevalence for GDM varies greatly. For instance, a study conducted in New York showed the prevalence of South-Asian (Indian, Sri Lankan, Pakistani, Fijian Indian) women having GDM are generally higher than the risk of South-East Asian (Cambodian, Vietnamese, Laotian, Thai, Filipino, Malaysian) women and the East-Asian (Chinese, South Korean, Taiwanese and Japanese) women. The prevalence of GDM in women who were born in Asian countries varied from 3.0% to 21.2%[28]. Many studies have shown Asian women had a much higher risk of GDM than women of United States Caucasian or Australian descent (Table 1). The highest risk appears to belong to women from South Asia and their adjusted relative risk is quoted by Savitz *et al*[28] to be as high as 7.1 (95%CI: 6.8 to 7.3).

Interestingly, studies have demonstrated that women who migrated from their native countries to a western society had a higher rate of GDM compared

Table 2 Diagnostic criteria for gestational diabetes mellitus prior to recommendations by the International Association of Diabetes in Pregnancy Study Group in 2010

	ADA-NDDG[65]	ADIPS[19]	NZSSD[66]	WHO (1999)[17]	CDA[67]	EASD[62]
Glucose load (g)	100	75	75	75	75	75
FPG (mmol/L)	5.3	5.5	5.5	7	5.3	6
1-h Glc (mmol/L)	10	-	-	-	10.6	-
2-h Glc (mmol/L)	8.6	8	9	7.8	9	9
3-h Glc (mmol/L)	7.8	-	-	-	-	-
Abnormal results to diagnose GDM	2 or more	1 or more	1 or more	1 or more	1 or more	1 or more

ADA-NDDG: American Diabetes Association National Diabetes Diagnostic Group; ADIPS: Australian Diabetes in Pregnancy Society; NZSSD: New Zealand Society for the Study of Diabetes; WHO: World Health Organization; CDA: Canadian Diabetes Association; EASD: European Association for the Study of Diabetes; FPG: Fasting plasma glucose; Glc: Glucose; GDM: Gestational diabetes mellitus.

to women of a foreign ethnicity but who were born in western countries[28]. However this trend did not apply to Japanese and South Korean women[29]. Table 3 summarises two large studies showing the prevalence of GDM amongst women of various ethnic groups who were born in western countries compared with those born in their native countries. Again the data seems to suggest women born in South Asian and Pacific Islander countries who have migrated to the United States had the highest rate of GDM than United States born women from the same ethnicity[29].

The demographic profiles of migrant mothers also varied among different ethnic groups. Studies had shown that Vietnam-born pregnant women with GDM who moved to Australia were more likely to be older, underweight and pregnant for the first time[30]. Similarly, Shah *et al*[31] found that United States Caucasian and Asian women with GDM were more likely to be over the age of 35 and have a higher education level. Compared with other Asian groups, Japanese and South Korean women have the lowest risk of GDM[12,29,32].

BODY MASS INDEX

Body mass index (BMI) has long been considered as a risk factor associated with the development of GDM[33]. Ethnic origin also appears to be a factor with a twofold higher rate in obese Hispanic women compared to African-American and Caucasian women[34]. Women with GDM from Pacific Islands had the highest pre-pregnant BMI (34.5 ± 8.0 kg/m^2), while those from South East Asia had the lowest (23.7 ± 4.8 kg/m^2)[25]. As BMI increases, the sensitivity of BMI to identify GDM in each racial/ethnic group decreases while the specificity increases. In a retrospective study of 24325 patients presenting at the University of San Francisco using a BMI of ⩾ 25 as a screening tool classified 76.8% of African-Americans with GDM in this category but only 24.9% of Asian women. Using a BMI cut-off of > 21.0 identified 91.5% of African-American women with GDM, 90.1% of Hispanic, and 79.8% of United States Caucasian, but only 68.4% of Asian women. African-Americans were shown to have the highest increased risk (OR: 5.1) of GDM when BMI > 25.0 was used as a screening tool, compared with US Caucasians (OR: 3.6), Hispanics (OR: 2.7) and Asians (OR: 2.3)[31].

Women from Asia were shown to have GDM during pregnancy despite having a BMI that is within or below normal range[30,32,35]. Therefore the role of BMI as a screening tool or risk factor for GDM in women from Asia is certainly questionable[31]. Hunsberger *et al*[15] found that Asian women had the greatest risk of having GDM compared to other ethnicities regardless of whether their BMI was greater or less than 26 kg/m^2. This population tend to have more visceral or central fat, which is a known risk factor for insulin resistance and cardiovascular disease[36]. Hence we would recommend screening pregnant Asian women for GDM regardless of their BMI.

A recent study on the interaction between maternal age and BMI showed the odds ratios for GDM development were significantly higher in women older than 30 years if they were Caucasian, older than 25 years if they were African and older than 20 years if they were South-Asians. This study also found that Africans and South-Indians were at higher risk of developing GDM irrespective of BMI[37].

MANAGEMENT OF GDM

Medical nutritional therapy (MNT) is the cornerstone in the management of GDM. The goal of MNT is to provide adequate calories and nutrients to meet the needs of pregnancy and consistent with maintaining normoglycaemia[5]. Yet there is very little consensus on a specific recommended dietary approach in the treatment of GDM[6,38,39]. A recent review of 6 randomised controlled trials in 250 women with GDM suggested that a diet higher in complex carbohydrate and fibre, low in simple sugar and saturated fat may be effective in preventing postprandial hyperglycaemia and avoid worsening insulin resistance and excess foetal growth[40]. Yet studies comparing low-glycaemic index (GI) with a high-GI or conventional high-fibre diet showed no difference in birth weight or adverse pregnancy outcomes[41,42]. Similarly a 2013 Cochrane Review assessing 11 different types of dietary advice for women with GDM was unable to conclude on which was the most suitable dietary advice. The specific diets analysed were low-and high-

Table 3 Studies comparing the prevalence of gestational diabetes mellitus among different ethnicities in women born in Western countries with women born in foreign countries

Ref.	Year	City/Region	Rate of GDM in ethnic groups born in Western country	Rate of GDM in ethnic groups who migrated from their native country to a western country
Savitz, Janevic, Engel, Kaufman and Herring[28]	1995-2003	New York City, United States	1.7% North African	7.5% North African
			3.1% Sub-Saharan Africa	5.9% Sub-Saharan Africa
			5.6% East Asia	6.3% East Asia
			4.3% South-East Asia and Pacific Islands	8.9% South-East Asia and Pacific Islands
			6.8% South Central Asia	14.5% South Central Asia
			3.4% Non-Hispanic Caribbean	7.1% Non-Hispanic Caribbean
			4.4% Hispanic Caribbean	5.3% Hispanic Caribbean
			4.0% Mexico	6.4% Mexico
			3.4% Central American	5.1% Central American
			3.1% South American	7.0% South American
Chu, Abe, Hall, Kim, Njoroge and Qin[29]	2005-2006	Up to 19 states in the United States	4.91% Japanese	3.27% Japanese
			5.54% Asian Indian	8.81% Asian Indian
			4.64% Chinese	6.25% Chinese
			5.95% Filipino	7.31% Filipino
			5.31% South Korean	4.92% South Korean
			5.16% Vietnamese	6.2% Vietnamese
			4.39% Other Asian	6.21% Other Asian
			5.82% Pacific Islander	8.38% Pacific Islander

GDM: Gestational diabetes mellitus.

carbohydrate, high-monounsaturated fat, fibre-enriched diet, low-, moderate-, and high-GI, and energy-restricted and unrestricted. Overall there were no significant differences seen in the rates of macrosomia, large-for-gestational age deliveries or caesarean section[39].

To achieve treatment goals, dietary plans should be prescribed by an accredited dietitian and should be culturally appropriate and tailored to the individual[5]. The ability to adjust the amount and type of carbohydrate by training patients in "carbohydrate counting" is important to achieve target blood postprandial glucose levels[38]. However, the amount of carbohydrate intake varies greatly between different ethnic and cultural groups. For instance, in South East Asia, rice is the staple food and this may pose major challenges for women from this background to curtail their rice intake. The diet for South-Asians is similarly heavily reliant on carbohydrate, and multiple sources of carbohydrate are often included at any one meal (*e.g.*, lentil, dhal, rice in combination)[43].

On the other hand, some women from the Middle East typically have a large meal in the afternoon with relatively smaller meals consumed at breakfast and dinner. They also have a tendency to delay breakfast till mid-morning and have dinner very late in the evening. Ramadan, an annual month of fasting observed by people of the Muslim faith, has significant impact on the timing of carbohydrate intake and meal portions. Ironically, it is the month where food consumption increases dramatically for Muslim communities as the daytime fasting is broken each evening with large banquets among family and friends which can last until dawn[44]. Although pregnant women are exempted from observing Ramadan, many pregnant women with GDM still choose to observe the important religious ritual with their family.

For Pacific Islanders, they also tend to have large servings of carbohydrate at main meals and multiple sources of carbohydrate at the one meal (taro, yam, cassava, green bananas, bread and rice)[45]. All these factors should be taken into consideration when prescribing MNT. An overly regimental dietary recommendation will therefore result in poor compliance to therapy and suboptimal glycaemic control.

Health literacy among women from different ethnic groups may be highly variable, and this could have a significant impact on management of GDM. A study of women with GDM in the United Arab Emirates showed they had little understanding of carbohydrate knowledge, but not significantly different to women who did not have GDM. Moreover 22% of women with GDM were not reviewed by a dietitian for nutrition counselling and 65% attended a dietitian only once or twice[46]. Furthermore, migrants in a Western society may also face huge challenges in managing their GDM. This could be related to language difficulty or their inability to adapt to an unfamiliar health system. A cross-sectional study conducted in Melbourne Australia showed that women coming from Vietnam had the poorest English skills and lowest education levels, with the greatest risk of misunderstanding GDM[47]. Women with a history of GDM were shown to have poor diet quality as determined by the Australian Recommended Food Score, and in particular women who spoke a language other than English had significantly poorer knowledge than those who spoke English only[48].

There were few studies that examined compliance to therapy for women with GDM. In an Australian study looking at failure-to-attend (FTA) rates of women with GDM, women who FTA more than once during their pregnancy had higher BMI, greater incidence of previous GDM and were more likely to be from non-Caucasian backgrounds[49]. Apart from language barriers,

women from non-Caucasian backgrounds may need greater resources and time from clinicians to help them understand their condition better in order to improve their adherence to treatment recommendations.

INSULIN THERAPY

The glycaemic targets set for the management of GDM may also differ between countries, and hence it would be difficult to compare the proportion of women requiring insulin therapy across different regions. From a database in south western Sydney, women from South-East Asia had the lowest prevalence for insulin therapy (37.2%), compared with Anglo-Europeans (56.7%)[25]. Despite having the highest 2-h glucose level on OGTT, women from South-East Asia also had the lowest need for rapid-acting insulin for the management of post-prandial hyperglycaemia. In that cohort, Pacific Islanders had the greatest need for insulin therapy, with 65% failing MNT. These women also had higher glycosylated haemoglobin (5.9% ± 0.9%, 41 ± 10 mmol/mol) at the time of diagnosis of GDM compared to women from South East Asia (5.4% ± 0.4%, 36 ± 4 mmol/mol)[25]. In a similar study conducted in Hawaii, women from Pacific Islands had the highest rate of commencement of insulin therapy (27.5%), while women from Chinese heritage had the lowest (11.1%)[11]. The higher percentage Pacific-Islanders requiring insulin before 20 wk of gestation in that study suggested that there could be a larger subset of Pacific-Islander women with previously undiagnosed type 2 diabetes.

FOETAL AND PERINATAL OUTCOMES

There is good evidence that treatment of women with GDM leads to better obstetrics and peri-natal outcomes[50]. GDM increases risks of adverse perinatal outcomes including large for gestational age, shoulder dystocia, surgically assisted delivery and hypertensive disorders in pregnancy[20]. In a 2013 systematic review commissioned by the United States Preventative Services Task Force and the National Institute of Health Office of Medical Applications of Research showed that treating GDM will result in a reduction in rates of preeclampsia, shoulder dystocia and macrosomia, but the benefits on preventing neonatal hypoglycaemia and averting long-term adverse metabolic outcomes of offspring are yet to be established[51].

Among Asian subgroups, Cambodian and Laotian women with GDM had increased odds of macrosomia when compared with Japanese women with GDM. However, South East Asian women had lower rates of foetal macrosomia when compared with United States Caucasian women but preterm delivery with preeclampsia occurred more often when compared with Japanese and United States Caucasian women[52]. Pacific Islanders have a higher rate of macrosomia than Asian or Caucasian women, but Asian neonates born with macrosomia had comparatively higher levels of NICU admission, need for intravenous dextrose treatment for hypoglycaemia and respiratory distress, although the overall numbers were small[10].

However another study from Ontaria Canada showed that mothers of Chinese heritage had a significantly lower risk of adverse outcome at delivery compared to South Asian mothers. Chinese women also had a lower risk of adverse maternal outcomes compared with the general population[53]. Several recent studies suggest infants born to mothers of non-Caucasian nationalities have lower adverse outcomes. A retrospective cohort study of 1865 adolescent women of different ethnicities born in a Californian University found that African-American, Hispanics and Asians had significantly lower rates of Caesarian delivery and low Apgar scores, while Asians and African-Americans had decreased rates of preterm delivery[54]. There is no evidence to suggest any increase in peri-natal mortality for a particular ethnic group within a health care system. In a study of neonates admitted to intensive care unit, the mortality of 9813 infants of Australian-born mothers was not different to the 2166 infants born from migrant mothers[55].

MATERNAL OUTCOMES

GDM represents relative beta-cell dysfunction which is caused by insulin resistance, revealed in response to the metabolic stress experienced during pregnancy[56,57]. Women from particular ethnic groups who have GDM may be more susceptible to developing diabetes in the future[2]. In particular, it appears that women with GDM from an Asian background who live in western societies are more likely than Anglo-European women to subsequently develop diabetes[30,58]. Moreover a recent meta-analysis showed that women from ethnic groups other than "non-Hispanic white" had a higher rate of GDM recurrence of 56% compared with 39% in "non-Hispanic white" women who experienced GDM[59].

A study of three ethnic groups of European, South Asian and Afro-Caribbean found that women who had a history of GDM had a range of metabolic abnormalities including beta-cell dysfunction with variable insulin resistance despite normal fasting blood glucose levels postpartum[60]. Similarly a study in the United Kingdom of 221 women with GDM or impaired glucose tolerance (IGT) showed Asian women were shown to have significantly higher rates of persisting glucose intolerance compared with Afro-Caribbean or Anglo-European women post-partum. Use of insulin in Asian women during pregnancy was also associated with postpartum IGT[14]. Development of type 2 diabetes mellitus in all ethnic groups was 3.5 times greater in women using insulin[58].

An Australian study found that all ethnic groups living in a multicultural region with a high percentage of foreign-born residents all had a high rate of post-GDM diabetes or IGT[2]. After a mean follow-up of 5.5 years, the study found that South Asians had the highest rate of either diabetes or IGT at 69%, more than the other

ethnic groups combined. South Asians and South-East Asians with either diabetes or IGT were also shown to have significantly lower BMI than Middle-Eastern or South European counterparts[2].

A recent large retrospective analysis of women who delivered at Massachusetts General Hospital between 1998 and 2007 showed that women with GDM were 2.45 times more likely to develop hypertension compared to women without GDM. Furthermore, African-American and Hispanic women with GDM had a higher risk of developing hypertension and Asian women had a lower risk compared to United States Caucasian women subsequent to pregnancy[61].

CONCLUSION

The increased risk of pregnant women developing GDM who belong to specific ethnic groups is widely acknowledged in the literature. This review highlights the major challenges in the provision of diabetes education and delivering MNT for GDM in an antenatal service where women may come from diverse ethnic and cultural backgrounds. Treatment involving MNT needs to be individually tailored and culturally sensitive, and insulin use may be more prevalent among some ethnic groups. Clinicians should appreciate that a "one size fits all" approach may not be appropriate in managing these women with GDM.

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REVIEW

Exercise guidelines for gestational diabetes mellitus

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Abstract

The prevalence of gestational diabetes mellitus (GDM) is increasing worldwide. This disease has many detrimental consequences for the woman, the unborn foetus and child. The management of GDM aims to mediate the effects of hyperglycaemia by controlling blood glucose levels. Along with pharmacology and dietary interventions, exercise has a powerful potential to assist with blood glucose control. Due to the uncertainty of risks and benefits of exercise during pregnancy, women tend to avoid exercise. However, under adequate supervision exercise is both safe and beneficial in the treatment of GDM. Therefore it is vital that exercise is incorporated into the continuum of care for women with GDM. Medical doctors should be able to refer to competently informed exercise professionals to aid in GDM treatment. It is important that exercise treatment is informed by research. Hence, the development of evidence-based guidelines is important to inform practice. Currently there are no guidelines for exercise in GDM. This review aims to assess the efficacy of exercise for the management of GDM in order to establish an exercise prescription guideline specific to the condition. It is recommended that women with GDM should do both aerobic and resistance exercise at a moderate intensity, a minimum of three times a week for 30-60 min each time.

Key words: Gestation; Pregnancy; Glucose; Physiology; Guidelines; Physical; Activity

Core tip: Exercise has been proven to be beneficial in improving pregnancy outcomes in women with gestational diabetes mellitus (GDM). However, there is currently no exercise guidelines published for this population. A review into research outcomes of exercise in pregnant women with and without gestation diabetes as well as guidelines pertaining to type 2 diabetes mellitus has been conducted. This review has shaped the first guidelines pertaining to exercise for GDM management.

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INTRODUCTION

The use of exercise as part of the continuum of treatment in patients with diabetic related disorders is accepted and widely encouraged[1]. One increasingly prevalent metabolic disorder is gestational diabetes mellitus (GDM). Although exercise prescription as treatment in this population group may be encouraged, a general exercise prescription guideline is lacking. Therefore the purpose of this review is to assess the efficacy of exercises currently being prescribed for the management of GDM in order to establish an exercise prescription guideline specific to GDM.

DEFINITION AND DIAGNOSIS OF GDM

GDM is defined as a "carbohydrate intolerance of varying degrees of severity with onset or first recognition during pregnancy"[2]. Other variants of this definition further refer to the period of onset of hyperglycaemia, specifically within 24-28 wk of gestation[3] and a natural dispelling of the hyperglycaemic condition after child birth[4].

The earliest record of hyperglycaemia during pregnancy is from the 1960's, when a research group led by O' Sullivan (and endocrinologist/gynaecologist) noted that hyperglycaemia in pregnant women was associated with poorer pregnancy outcomes and a higher occurrence of type 2 diabetes in the years ensuing pregnancy[4]. In 2013, the World Health Organisation (WHO) released a classification and diagnostic criteria for GDM (Table 1)[5]. The new criteria was developed to take into account a quantifiable relationship between hyperglycaemia and adverse short-term pregnancy outcomes for both mother and newborn, in light of findings from the study of Hyperglycaemia and Adverse Pregnancy Outcomes (HAPO)[6]. This diagnostic guideline can be used throughout pregnancy and can distinguish GDM from diabetes mellitus in pregnancy (Table 1)[5]. However, as the new criterion recommends lower fasting plasma glucose levels than what has been previously used, the WHO anticipated as increase in the number of pregnant women diagnosed with GDM[5]. The effects of these criteria changes are yet to be evaluated, especially in the area of pregnancy outcomes.

RISK FACTORS FOR GDM

There is a range of risk factors that increase the chance of developing GDM. Ethnicity may play a role in GDM development as elevated incidences have been reported in certain ethnic subgroups. In the United States epidemiological studies have reported a higher incidence of GDM in African Americans, Native Americans, Hispanics and Orientals than in non-white Hispanic women[7-9]. In Australia, the prevalence of GDM was found to be higher in Aboriginal Australians as well as women who were born in Asia and India[10-12].

In Europe, a large scale epidemiological study (n = 11205) in London found that women of ethnic minority groups had higher prevalence of GDM[13]. When compared to White women, relative risks ranged from 3.1 for Black, 5.9 for miscellaneous, 7.6 for South Asian and 11.3 for Indian women[13]. Asian women living in Asia have less proportional incidence than Asian born women living in other continents[14]. Indian women living in urban areas have greater observed incidence that those living in rural areas of India[15].

Furthermore, non-modifiable risk factors include greater maternal age (defined as 35 year of age plus)[16,17], polycystic ovarian syndrome, family history of diabetes mellitus and pregnancy induced hypertension[17]. Incidence of GDM has also been 30%-60% greater in women who have experienced the disease in a previous pregnancy[18-22]. In a 16 year longitudinal retrospective study of 651 Canadian women who had GDM during their first pregnancy, 35% developed GDM in their second pregnancy[23]. Greater pre-maternal weight was a strong predicting factor of GDM re-occurrence in ensuing pregnancies[23].

This finding leads into a discussion of lifestyle related factors that are largely modifiable. Factors such as overweight and obesity can be modified. Weight gain during pregnancy was investigated using a nested-case control study of 1145 women[24]. Findings suggested that subjects with greater weight gain during pregnancy (0.27-0.41 kg/wk or more) had an increased risk of developing GDM by 43%-74%. This effect was further exacerbated in overweight and obese women[24]. Furthermore poor diet and nutrition are reported as mediators of increasing maternal weight and risk of GDM[25-27]. Diets particularly high in refined sugars, with a high glycaemic index and fat content have been thought to increase the risk of GDM and hypertension during pregnancy[25,28]. However, the majority of studies reporting these findings are small and have not been able to provide conclusive evidence on the role of diet in increasing the risk of GDM[25,28]. Even so, one large prospective study (n = 13475), investigated the consumption of sugar sweetened beverages and incidence of GDM. After a 10 year follow up and 860 cases of GDM, excessive consumption ($\geqslant$ 5 servings a week) of sugar sweetened cola was found to increase the risk of GDM by 22%[29].

In a population based longitudinal study of 824 women, hypertension was found to increase relative risk of developing GDM up to twice as much (relative risk 2.03) as women without hypertension[30]. The relationship between hypertension and GDM was confirmed in a Danish study of 215 women, in which higher rates of GDM was found in those with hypertension[31]. Literature surrounding the pathophysiology of hypertension and gestational diabetes does not clearly underpin the

Table 1 Diagnostic criterion for gestational diabetes mellitus (WHO 2013) and diabetes mellitus in pregnancy (WHO 2006)[5]

	Gestational diabetes mellitus	Diabetes mellitus in pregnancy
Fasting plasma glucose level	⩾ 5.1-6.9 mmol/L	⩾ 7.0 mmol/ L
	OR	OR
75 g oral glucose tolerance test levels	1 h: ⩾ 10.0 mmol/K 2 h: ⩾ 8.5-11.0 mmol/L	1: Not required 2 h: ⩾ 11.1 mmol/L
Random plasma glucose level	Not required	⩾ 11.0 mmol/L

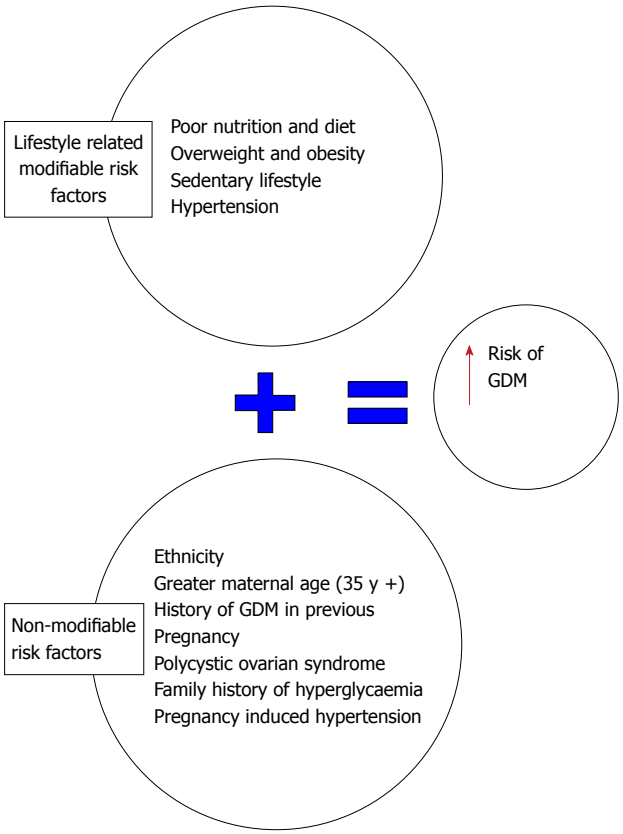

Figure 1 Risk factors for gestational diabetes mellitus. GDM: Gestational diabetes mellitus.

mechanisms that cause such complications. However, it has been suggested that hypertension during pregnancy may heighten insulin resistance, alter immune responses and inflammatory pathways[32]. These responses further encourage hypertension and hyperglycaemia, reminiscent of pathways in the metabolic syndrome[32,33].

Sedentary behaviour and lifestyles characterised by low levels of physical activity have also been shown to increase the risk of GDM. In the largest reported study documenting physical activity and sedentary behaviour in relation to risk of GDM, Zhang *et al*[34] reviewed cases of 21765 women's pregnancies, 1428 of whom had GDM. They controlled for dietary factors and other covariates and found inverse relationships between vigorous activity, higher weekly physical activity levels and risk of GDM[34]. Vigorous activity and brisk walking both had protective effects against developing GDM (RR = 0.77 and RR = 0.66 for each respectively). Women who were sedentary had a greater that two fold increase in developing GDM (RR = 2.30)[34]. A more recent randomised control trial involving pregnant women had an exercise group (n = 40) which engaged in moderate land based resistance activity combined with aquatic aerobic activity[35]. The control group (n = 43) was not given physical activity advice or exercise supervision. During 24-28 wk of gestation the women underwent a 50g maternal glucose screening test of which the exercise group had significantly better glucose levels (5.76 ± 1.13) that the control group (7.05 ± 1.73 mmol/L)[35]. A case-control study by Dempsey *et al*[36]found a large reduction in GDM diagnosis in non-diabetic women who participated in recreational physical activity in the first 20 wk of pregnancy by 48%-78%. Further prospective studies of 909 non-diabetic American women, found that recreational exercise leading up to pregnancy, when performed for at least one year can induce a 56%-76% reduction in the risk of developing GDM[37]. A large meta-analyses investigating seven pre-pregnancy and five early pregnancy studies found that pre-pregnancy exercise gave a pooled odds ratio of 0.45, a high protective effect against GDM[38]. Furthermore, exercise in early pregnancy was also significantly protective of developing GDM with an odds ratio of 0.76[38]. For a summary of risk factors see Figure 1.

EFFECTS OF GDM IN MOTHER AND CHILD

GDM affects the health of the women, the foetus and even after birth, the baby or child. Hyperglycaemic placental environments increase the risk of traumatic pregnancies influenced by macrosomia (larger than usual birth weight)[39,40]. This in turn increases the risk of the baby having shoulder damage during birth[40]. Macrosomia can be further exacerbated by excess levels of insulin circulating in the placenta[3,41]. This is due to the increased growth effects of insulin on the foetus[41]. Therefore care must be taken when prescribing anti-glycaemic maternal medication. The uses of different types of medications are still being investigated and there is a body of evidence yet to be filled regarding the direct impact of anti-glycaemic agents on foetal health. However, reviews have suggested that the use of insulin secretagoues is the safest form of pharmacological treatment in GDM, as they have little to no perfusion across the placenta[41-43]. However, oral hypoglycaemic agents including metformin and glyburide have been used as alternative pharmacological treatment to insulin therapy[44,45].

Further complications for the baby directly after birth include acute breathing difficulty, jaundice and nerve palsy[46-48]. Babies born of women with poorly controlled GDM are likely to experience hypoglycaemia after birth due to an immediate impairment of environmental

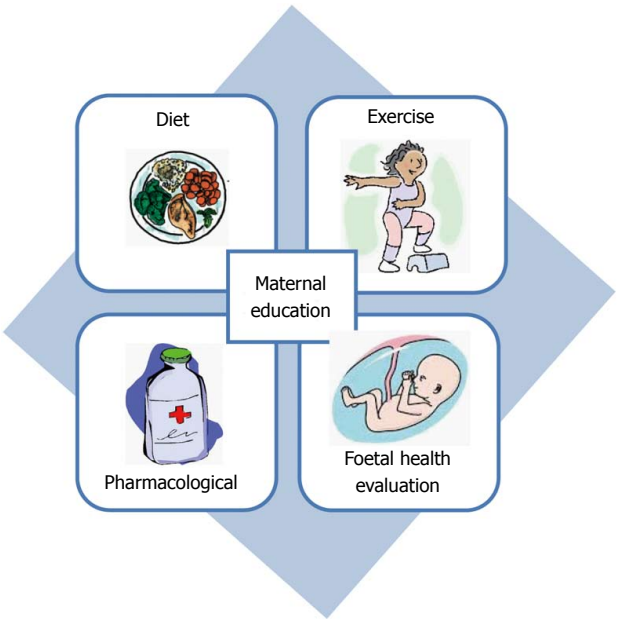

Figure 2 Gestational diabetes mellitus quintet management model.

glucose[46,49]. Because of the complications presented, babies are more likely to be admitted to intensive care units and endure longer hospital stay times[48,49]. As the child grows they are more likely to develop obesity as well as metabolic disorders such as type 2 diabetes[50,51].

Traumatic births caused by the compounding effects of GDM also present complications for the women's immediate health[47]. Women are more likely to undergo an emergency caesarean section, particularly with the presence of preeclampsia[49]. Preeclampsia is a combination of high blood pressure and excessive protein in urine, also the second leading cause of maternal death[49]. Due to the increased size of the baby, they are also more likely to have a longer active labour times, instrumental vaginal delivery as well as third degree perineal trauma and tearing[49,51]. These traumatic events generally lead to post-partum haemorrhage and hence longer hospital stay times[49]. Furthermore, women with GDM have greater weight retention post-partum leading to a greater risk of overweight and obesity[51,52]. This has also been shown to correlate with increased risk of developing chronic hypertension, type 2 diabetes and GDM is ensuing pregnancies[49,51,52].

Because of the vast effects of GDM on the health of both mother and child, the management of GDM is critical in minimising the effects of hyperglycaemia during pregnancy.

GENERAL MANAGEMENT OF GDM

The primary aim of GDM management is to optimise glucose control and improve pregnancy outcomes[53]. Generally speaking the initial management of GDM involves diet modification and implementation of an exercise regime[49,54]. If adequate glucose control has not been achieved, the woman will generally be prescribed anti-diabetic medications to directly reduce blood glucose levels maternally and hence indirectly for the foetus[42].

Although it is not a treatment method, constant evaluation of the foetus' health and development is recommended to continually assess for deformities and macrosomia[54]. This includes foetal surveillance using ultrasound and Doppler of umbilical blood flow measurement[49,54,55]. In a large randomly controlled trial, 1000 women diagnosed with GDM were randomly assigned gestational diabetes care (n = 490) or routine care (n = 510). The gestational diabetes care group received dietary advice, blood glucose monitoring and insulin therapy. The control group received no standard pregnancy care. Pregnancy outcomes were assessed and after controlling for various factors including ethnicity and age, the diabetes care group had lower rates of serious perinatal complications (1% *vs* 4%)[49]. However, this intervention did not include maternal exercise or education. There were also no protective effects on admittance to the intensive care unit, induced labour or risk of caesarean delivery. A more recent and larger meta-analysis by Poolsup *et al*[56] investigated ten studies regarding the outcomes of GDM treatment methods including pharmaceutical and dietary care. It was found that such treatment significantly reduced the risk of macrosomia (RR = 0.47), shoulder damage during birth (RR = 0.42) and gestational hypertension (RR = 0.68). However alongside the absence of exercise from these treatments, there was no change in the risk of neonatal mortality, neonatal hypoglycaemia, birth trauma, premature births, preeclampsia, caesarean section and induced labour[56].

The recommended quintet approach for GDM (Figure 2) includes maternal education, diet modification, exercise, pharmacology and foetal surveillance. This has been developed in light of the confounding evidence of increased positive pregnancy outcomes in studies of these areas independently. A study investigating the efficiency and practicality of this complete model of maternal and foetal care is yet to be investigated.

ROLE OF EXERCISE IN GDM MANAGMENT

In regards to evidence specific to GDM treatment, exercise has been shown to be an effective tool in glucose control which may prevent, reduce or delay the need for insulin[57,58]. Tight glucose control is considered especially important in the gestational patient, considering the increased risk of poor health outcomes for both mother and child in the presence of hyperglycaemia. For future ramifications, it has been found that any degree of abnormal glucose homeostasis during gestation can also independently predict diabetic re-occurrence in women with GDM[57].

Although currently there are no GDM specific exercise prescription guidelines published, research has been conducted in general pregnancy and exercise.

Table 2 Absolute and relative contraindications for exercise during pregnancy[75,82]

Absolute contraindications	Relative contraindications (aerobic exercise)
Restrictive lung disease	Heavy smoking
Ruptures membranes	History of extremely sedentary lifestyle
Preeclampsia	Orthopaedic limitations
Pregnancy-induced hypertension	Poorly controlled hypertension
Premature labour during current pregnancy	Extreme morbid obesity
Persistent bleeding (second or third trimester)	Extremely underweight (BMI < 12 kg/m^2)
Incomplete cervix or cerclage	Poorly controlled type 1 diabetes
Placenta previa (placental implanting into lower uterus) after 26 wk of gestation	Chronic bronchitis
	Severe anaemia
Hemodynamically significant heart disease	Unevaluated maternal cardiac arrhythmia
High order multiple gestation (≥ triplets)	Intrauterine growth restriction in current pregnancy
	Poorly controlled seizure disorder
	Poorly controlled hyperthyroidism
	Previous spontaneous abortion
	Anaemia (hb < 100 g/L)
	Twin pregnancy after 28 wk
	Malnutrition or eating disorder

BMI: Body mass index.

There has been no suggestion of the need to any extra precautions than the precautions taken when exercising pregnant women without GDM. However, considering the added hyperglycaemia, the same considerations and precautions concerning type 2 diabetes should also be considered when exercising women with GDM. Hence the FITT (frequency, intensity, time/duration and type) principles of exercise examined and presented in this review will take into consideration research including women with GDM, without GDM and type 2 diabetes. Given the lack of large cohort studies implementing exercise as management of GDM, recommendations have been drawn from exercise in pregnancy guidelines and exercise in type 2 diabetes guidelines.

For women who were previously sedentary before pregnancy, it is advised that they consult their medical practitioner who may asses their suitability to exercise. It is recommended that a suitability qualified exercise physiologist be actively involved in exercise prescription and delivery. This person would then be able to liaise with the medical practitioner to apply advice regarding suitability. As with any clinical population there are some contraindications to exercise in pregnancy. The absolute contraindications as recommended by the American Congress of Obstetricians and Gynaecologists (ACOG) are medical conditions which may be exacerbated by engaging in exercise. It is important that to educate patients that these conditions are not caused by exercise and until the condition is stabilised, they should not engage in exercise. Furthermore, ACOG has developed relative contraindications for engaging in aerobic exercise during pregnancy. Clinical knowledge and expertise must be applied when assessing each individual situation in regards to exercising with relative contraindications. It is recommended that advice from the medical practitioner is carefully interpreted by the exercise physiologist to determine if the benefits out way any risks of exercise. Both absolute and relative contraindications for exercise in pregnancy are summarised in Table 2.

BENEFITS OF EXERCISE DURING PREGNANCY

Benefits to the mother

Exercise has been proved to be a beneficial therapeutic tool during pregnancy. Records as early as the 17th and 18th Centuries have shown encouragement of exercise during pregnancy as it was thought to ensure good health and prevent miscarriage[59]. Further in the late 18th Century maternal physical activity was thought to help encourage an easier labour and reduce the baby size, also advantageous during delivery[60]. In the early 20th Century particular the 1920's and 1930's, scientific studies began to investigate the impact of physical activity on pregnancy outcomes. These studies found inverse relationships between birth weight and household physical activity[61]. In the 1920's studies began to inform prenatal exercise programs with benefits recorded as increased ease of labour, improved muscle tone, increased foetal oxygenation and facilitating post-partum weight loss[62].

Key epidemiological studies came later in the 1990's. Clapp *et al*[63] found that women who exercised during pregnancy had babies with a significant lower birth weight than those who had decreased their physical activity during pregnancy. In 1991 Bung *et al*[64] investigated the use of exercise in women with GDM. This randomised control trial was one of the first of its kind and findings were imperative to influence future research into the efficacy of exercise in GDM management. Seventeen of the twenty-one women in the exercise group, of whom were all previously insulin dependent were able to maintain normal glucose levels without using insulin[64]. Maternal complications did not differ between the

Table 3 Benefits of maternal exercise for the foetus and the child

Benefits to the foetus[100-104]	Benefits to the foetus[1,58,73,104,105]
Lower heart rate response to acute maternal exercise	Lower birth weights
Increased amniotic fluids	Increased gestational ages (lower risk of preterm birth)
Increased in placenta viability and volume	Improved neurodevelopment and lower body fat percentage
Increase in vascular function	Infants have higher behaviour regulatory ability and orientation
Faster placental growth and greater villous tissue	At the age of five children have less body fat, higher general language intelligence and oral language
Higher tolerance to labour	

Table 4 Modified heart rate target zone for aerobic exercise in pregnancy[82,95]

Maternal age	Heart rate target zone (beats/min)	Heart rate target zone (beats/10 s)	Heart rate target zone (beats/min) (SOwt/SOb)
< 20	140-155	23-26	-
20-29	135-150	22-25	102-124
30-39	130-145	21-24	101-120
⩾ 40	125-140	20-30	-

SOwt: Sedentary overweight; Sob: Sedentary obese.

exercising group and the control group. Exercise was now deemed to be safe and advantageous for glucose control for women with GDM[64]. These findings were also confirmed by Jovanovic-Peterson *et al*[65] in a smaller study of women with GDM utilising exercise and diet (n = 10) and those using diet alone (n = 10). The findings of this study concluded that women engaged in diet plus exercise had lower fasting plasma glucose after 6 wk of training than women who underwent the diet only intervention (diet = 4.87 mmol/L, exercise and diet = 3.89 mmol/L)[65]. This was further confirmed in a more recent study in which physical activity and diet interventions resulted in a lessened dependence on insulin for glucose control in women with GDM[66]. Since there is little more exercise interventional trials conducted in women with GDM, this review is also informed by exercise in pregnancy.

Multiple studies have reported the positive effects of exercise on decreased lower back pain in pregnant women, two of which were recent randomised controlled trials[67,68]. Other physiological studies have reported exercise in pregnant women to improve cardiovascular functions such as fitness, blood pressure, and peripheral oedema[69]. Preeclampsia has also been show to decrease with an increase in physical activity[70,71]. As previously demonstrated exercise may decrease the risk of developing GDM and type 2 diabetes[36,72]. Furthermore, by increasing blood glucose control, exercise reduces the vast effects of hyperglycaemia on the women, foetus and child (see above section Benefits to the mother). As pregnancy is a period associated with physiological and psychological change, the benefits on mood and psychological wellbeing are also well documented. Due to a limitation in weight gain and fat retention, exercise has also been shown to improve self-image[73]. The ACOG have also recently report an improvement in constipation and bloating as well as fatigue and insomnia[74].

Benefits to the foetus and child

Pregnancy outcomes are largely associated with foetal health and upon birth, the health of the child as well. Maternal exercise has also been shown to provide significant benefits to both the health of the foetus and the child. Because neonatology and paediatrics is beyond the scope of this review, these findings are summarised in the Table 3.

EXERCISE GUIDELINES

Type

Safety during pregnancy is paramount and studies have shown a variety of exercises ranging from low exerting forces such as Yoga to higher exerting forces such as aerobic classes and jogging can be safe for both mother and foetus[75]. Considering the importance of safety, it is advised that some forms of exercise should not be practiced during pregnancy, including the following: recreational sports with increased risk of forceful contact or falling (*i.e.,* basketball, rugby, horseback riding and gymnastics), exercising in a supine position after the first trimester (may obstruct inferior vena cava flow), motionless standing and scuba diving (risk of foetal decompression sickness)[75]. Recreational physical activity is encouraged and has been shown to improve general wellbeing, pregnancy outcomes[76]. Furthermore maternal mood and mental health have been shown to benefit from recreational physical activity[76] (Table 4).

Programmed exercise is also very important in pregnancy and is vital to aid in glucose control for women with GDM[76].

Exercise guidelines for pregnancy stress the prescription of aerobic exercise and to a lesser extent the prescription of resistance strength training. Women who regularly exercise during pregnancy have more positive pregnancy outcomes and fewer negative adverse events[77]. However, there is little evidence of what is the physiological role of aerobic exercise in these relationships[77]. The only truly quantifiable relationship thus far is that of aerobic exercise and significantly improved maternal fitness during pregnancy[77]. Positive foetal outcomes are yet to be quantified as the majority of this research area has focused on foetal safety during exercise[75]. There is a general agreement that appropriate exercise does not induce any harm on the

foetus[75]. However, in regards to elevate fasting glucose, aerobic exercise can indeed reduce blood glucose levels in individuals with hyperglycaemia, potentially reducing and delaying the need for insulin medication[78]. These effects may last for more than 24 h but less than 72 h. Furthermore, following aerobic exercise insulin levels also drop, reducing the chance of hypoglycaemia[78]. However, after an intense bout of exercise, a hyperglycaemic response may be observed for up to 2 h post exercise[78-80]. This may be important to consider when measuring blood glucose levels after exercise.

Aerobic exercise can consist of any activity that uses large muscle groups in a continuous rhythmic manner, *i.e.,* walking, jogging, aerobic dance, swimming, hydrotherapy aerobics, rope skipping, hiking, rowing, *etc*[75]. However, clinical judgement should be exercised when choosing the appropriate and practical mode of aerobic exercise. This is particularly important in the first stages of an exercise program if intensity is to be tightly controlled (see below in intensity).

In addition to aerobic exercise, resistance strength training (*i.e.,* weightlifting) and flexibility exercise are also beneficial and safe for gestational women and foetus[75,81,82]. Although the Royal College of Obstetricians and Gynaecologists (RCOG), ACOG, the Society of Obstetricians and Gynaecologists of Canada (SOGC) and Canadian Society for Exercise Physiology (CSEP) all recommend the use of resistance training for pregnant women, they are yet to provide specific guidelines for practice. However, Hall *et al*[83] investigated the effects of moderate intensity strength training in healthy pregnant women. They used a protocol of 12 reps and one set of 8-10 exercises and found pregnancy outcomes were improved with no adverse effects to foetal health[75,83]. Women who used resistance band exercise training at a moderate intensity three days a week had improved glucose control. This was reflected in lower capillary glucose levels and significantly less users of insulin (n = 18 control *vs* n = 7 exercise group)[84]. Pregnancy specific pelvic floor exercise training has also been shown to reduce incontinence and bladder weakness after pregnancy[69]. However, in the treatment of elevated fasting glucose, the American College of Sports Medicine (ACSM) and Exercise and Sports Science Australia (ESSA) both recognise that resistance training lowers fasting blood glucose levels for 24 h after exercise[78,85]. This response is further exaggerated with an increase in training volume and intensity[78,85]. Mode of exercise used in resistance training may include but is not limited to, resistance machines, free weights and body weight exercises[78,85].

The ACOG reports hydrotherapy exercise to be considered safe during pregnancy with the potential to improve positive outcomes and pregnancy management[75]. It has been shown that aerobic water based exercise at a moderate intensity may improve fitness, strength and decrease peripheral oedema[75]. With the added effects of increased buoyancy, hydrotherapy may minimise the risk of musculoskeletal joint injuries and provide a pain relieving manner of exercise for suffers of pregnancy induced lower back pain[1,75]. Thermoregulatory issues should also be considered. Although significant research has not yet been conducted on humans, animal studies have shown that an increase in core temperature by as little as 1.5 ℃ during embryogenesis (in early stages of pregnancy) may result in major congenital malformations[86]. Although these findings have not yet been supported in human studies, it may highlight the importance of remaining adequately hydrated and exercise in environments that are cool, shaded and well ventilated. During pregnancy it is important to note that core temperature is already raised due to an increase in the basal metabolic rate[87]. Furthermore during exercise increases in body temperature strongly correlate with work intensity[87]. Therefore, prolonged intensity workouts that encourage temperature fluctuations and an accelerated loss of fluid through perspirations may need to be avoided[75].

Both ACSM and ESSA recommend that combined aerobic and resistance exercise are more effective if blood glucose management, body composition improvement and fitness outcomes[78,85]. However, training using both of these modes may be more time consuming and greatly dependent on the individual's comorbidities, complications, accessibility to equipment and preference[88-90]. Even so, combination training shows improvements in blood glucose control utilising different physiological mechanisms that may be of greater use when activated together[78]. Resistance training resulting in an increased muscle mass can increase blood glucose uptake independent of intrinsic insulin response as insulin does not have influence on musculature glucose uptake[84,88]. Aerobic training increases insulin stimulatory action and thus increases blood glucose uptake *via* a different pathway[88]. Activating both of these metabolic pathways may be more physiologically beneficial than utilising only one pathway or exercising using only resistance training or aerobic training[78].

Performing a warm up before exercise is recommended for all clinical populations[91]. Warm up's of between 5-10 min at a low to moderate intensity using aerobic activities can increase body temperature and reduce post-exercise muscle soreness and stiffness[91]. Warm ups are an important stage in exercise, as physiological systems gradually adjust to meet the bioenergetics and biomechanical demands of the working component of the exercise session[91]. Performing a post exercise cool down is recommended if vigorous exercise is performed to reduce the risk of a vasovagal response which may lead to syncope[92]. Stretching and flexibility training is distinct from the warm up or cool down phase and can be performed after either[91]. Although there are limited studies investigating the role of warm up and cool down phases in exercise during pregnancy, there is no evidence to suggest that this may cause any harm. Considering the general benefits implicated for most populations,

Table 5 Exercise guidelines for gestational diabetes mellitus

Type of exercise	Intensity	Duration	Frequency
Aerobic (large muscle activities in a rhythmic manner) *e.g.*, walking, running, swimming and cycling	Moderate 60%-90% of APHRM RPE 12-14 Previously sedentary Owt/Ob should begin training at 20%-30% of APVO2R RPE 12-14 Vigorous RPE 14-16	⩽ 30 min continuously (up to 45 min if self-paced)	No more than two consecutive days without exercising
Resistance (multi joint exercises, large muscle groups) *e.g.*, dumbbells, resistance band and pregnancy Pilates	Moderate 50% 1RM 5-10 exercises 8-15 repetitions 1-2 sets	60 min	At least 2 but ideally 3 times a week

APHRM: Age predicted heart rate maximum; RPE: Rate of perceived exertion; Owt: Overweight; Ob: Obese; APVO2R: Age predicted VO_2 reserve; RM: Repetition maximum.

it can be safe to assume the same would apply for pregnant women.

Frequency and duration

When prescribing exercise it is important to take into consideration the woman's previous physical activity history, cardiorespiratory fitness and strength[1]. For women who were previously sedentary it may be more convenient for them to start an exercise program in the second trimester, after which most of the initial discomforts of morning sickness, nausea and fatigue have settled down[81]. This is recommended so that extra discomforts of initiating an exercise program may not in turn impair adherence or compliance. Yet, as previously discussed, exercise in early pregnancy can reduce the risk of GDM, therefore sooner the woman can comfortably exercise the better[35-37]. Women with little physical activity history should begin with 15 min of continuous aerobic exercise three times a week with a graded increase to 30 min at least four times a week[78]. This was also previously recommended in the 2002 ACOG and is also supported in by the Society of Obstetricians and Gynaecologists of Canada (SOGC) and Canadian Society of Exercise Physiologists (CSEG) guidelines[75,82]. There is no recommendation of and upper limit of time spent performing aerobic exercise, but the ACOG advises against exercising for more than 45 min continually because of a risk of increased foetal temperature[75]. However this temperature rise is seen to be negligible when the exercise is self-paced in an environment that has adequate temperature control[75]. Exercise guidelines for Type 2 Diabetes from the American College of Sports Medicine (ACSM) and Exercise and Sports Science Australia (ESSA) are generally the same as the pregnancy guidelines. However ACSM and ESSA have an additional note that there exercise should be conducted with no more than 2 consecutive days between aerobic exercise sessions[78,85]. This is due to the transient improvement of insulin action and passive glucose uptake after exercise for up to 48 h[78,85]. In regards to resistance training, ACSM and ESSA recommend a minimum of twice a week on non-consecutive days and ideally three times a week[78,85]. Each training session should include 5-10 (ACSM) or 8-10 (ESSA) exercises involving the major muscle groups (upper body, lower body, and core) and 10-15 repetitions (ACSM) or 8-10 repetitions (ESSA) each set at a minimum of one (ACSM) or two (ESSA) sets for strength gains, but up to four sets for optimal glucose uptake and strength gains. Considering that it is recommended that women do not train for optimal gains during pregnancy, up to three sets at moderate intensity may be more appropriate.

Intensity

During pregnancy, the majority of guidelines indicate the use of moderate intensity, but even low intensity exercise such as Yoga and Tai-Chi has shown benefits on mood, balance, lower back pain and urinary incontinence[93,94]. As cardiorespiratory fitness is vitally important in encouraging positive outcomes during pregnancy and post pregnancy, moderate aerobic exercise is highly recommended[1,94]. Heart rate is a relatively simple way to prescribe aerobic exercise in a manner that corresponds with perceived exertion and thus intensity. However during pregnancy, heart rate is elevated by 10-15 beats and is blunted at maximal exercise levels[82], RCOG, SCOG and CSEP have all recommended the use of a modified heart rate target zone developed by the CSEP, when prescribing moderate intensity aerobic exercise (see Table 5)[1,82]. This target zone aims for an exercising level of 60%-90% of age predicted maximal heart rate. Furthermore, Davenport *et al*[95] have developed and validated an exercise target heart rate zone especially for sedentary overweight and obese pregnant women (Table 5). This model aims to exercise previously sedentary pregnant women at 20%-39% VO_2 reserve for as recommended by ACSM. Even so, it is interesting to know why this was only recommended for sedentary overweight and obese women and not previously sedentary normal weighted women. Furthermore, during

pregnancy heart rate variability increases[75]. Therefore, ACOG recommends that prescribers exercise caution using heart rate to guide intensity and should consider using Borg's Modified Rate of Perceived Exertion Scale instead[75]. Exercisers are recommended to aim for a working intensity of 12 to 14 (somewhat hard) on a 6-20 scale[75]. McMurray also reported that women who self-paced exercise intensity would gradually reduce intensity as pregnancy progressed[96].

High intensity short duration interval training has also been shown to be safe with showing no added complications during pregnancy but caution should be exercised for previously sedentary women[75,82,97]. Furthermore, it may have protective effects from the foetus developing macrosomia and risk of preterm birth[98].

ACSM's also recommends high intensity interval training for those exercising using moderate intensity and are in need of more glucose control[78].

Resistance strength training has also been shown to positively influence the mother's general health and pregnancy outcomes[81,99]. It is especially important to consider the physiological changes during pregnancy when prescribing resistance training and that high intensity resistance training should be avoided. Changes include increased urinary tract pressure (cause of urinary incontinence) and increased laxity in joints[69]. Therefore care must be taken not to induce Valsalva manoeuvres that may increase the risk of injury or adverse event[82]. There are few recommendations for resistance training guidelines during pregnancy, due to a lack of large quality studies. Therefore in accordance to other general pregnancy exercising guidelines, a recommended intensity of a moderate level is suggested. In regards to impaired fasting glucose, ACSM recommends strength training at a moderate (50% of 1-repitition maximum) or vigorous (75%-80% of 1-repitition maximum) intensity for optimal gains in strength and insulin action[78]. ESSA generally recommends similar intensity of resistance exercise, yet with a greater inclination encourage vigorous intensity in light of dose related glucose control[85]. Considering the added physiological changes in pregnant women, a moderate intensity training model is more appropriate. Furthermore, to avoid injury a slow progression of intensity, frequency and duration of strength training sessions occur[78].

PRECAUTIONS AND RECCOMENDATIONS TO TERMINATE EXERCISE

Although there are vast benefits from exercising during pregnancy, some precautions need to be observed to encourage safety for both mother and child. As previously noted, the ACOG has advised against some forms of exercise including the following: recreational sports with increased risk of forceful contact or falling (*i.e.,* basketball, rugby, horseback riding and gymnastics), exercising in a supine position after the first trimester, motionless standing and scuba diving[69,75].

Furthermore, if any of the following warning signs occur, it is advised that exercise should be terminated: vaginal bleeding, dizziness, headache, chest pain, muscle weakness, preterm labour, decreased foetal movement, amniotic fluid leakage, calf pain or swelling and dyspnoea without exertion. It is important to regain stability of the mother's and foetus' condition as soon as possible. Treatment and advice from a medical practitioner should be incorporated in the exercise program[69,75].

Exercising individuals with impaired fasting glucose presents its own sense of challenges and special considerations. Preventative measures should be in place to minimise the risk of an adverse event occurring and not prevent individuals from exercising. One especially important possible complication, however rare is hypoglycaemia. It is suggested that continual self-monitoring of blood glucose levels with physician consultation should be encouraged. Furthermore, if at pre-exercise the blood glucose level is $\leqslant$ 4.0 mmol/L this should be considered low and exercise should not begin till administration of some long and short acting glucose in food or drink[85]. In order to take advantage of the hyperglycaemic effect of food, it may be advantageous to exercise an hour after a meal[85]. It also may be important to consider taking insulin medication well before exercise to further reduce the risk of hypoglycaemia.

CONCLUSION

All pregnant women should engage in physical activity and may benefit from planned and programmed exercise. Women with GDM have extra physiological challenges that when left unattended to, have the potential to increase negative pregnancy outcomes for both mother and child. When used effectively, exercise can be used as a tool of treatment as part of the continuum of care for women with GDM. General guidelines encourage these women to engage in moderate intensity aerobic and strength training along with recreational physical activity. Exercise programs should be tailored by appropriately trained and qualified professionals (*e.g.,* Exercise Physiologists) who have knowledge, training and experience to understand the individual's physiological needs and associated risks.

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REVIEW

Indicators of glycemic control in patients with gestational diabetes mellitus and pregnant women with diabetes mellitus

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Abstract

Recently, it has become clear that mild abnormal glucose tolerance increases the incidence of perinatal maternal-infant complications, and so the definition and diagnostic criteria of gestational diabetes mellitus (GDM) have been changed. Therefore, in patients with GDM and pregnant women with diabetes mellitus, even stricter glycemic control than before is required to reduce the incidence of perinatal maternal-infant complications. Strict glycemic control cannot be attained without an indicator of glycemic control; this review proposes a reliable indicator. The gold standard indicator of glycemic control in patients with diabetes mellitus is hemoglobin A1c (HbA1c); however, we have demonstrated that HbA1c does not reflect glycemic control accurately during pregnancy because of iron deficiency. It has also become clear that glycated albumin, another indicator of glycemic control, is not influenced by iron deficiency and therefore might be a better indicator of glycemic control in patients with GDM and pregnant women with diabetes mellitus. However, large-population epidemiological studies are necessary in order to confirm our proposal. Here, we outline the most recent findings about the indicators of glycemic control during pregnancy including fructosamine and 1,5-anhydroglucitol.

Key words: Glycemic control; Hemoglobin A1c; Glycated albumin; 1,5-anhydroglucitol; Fructosamine; Gestational diabetes; Diabetes mellitus; Pregnancy

Core tip: In patients with gestational diabetes mellitus (GDM) and pregnant women with diabetes, stricter glycemic control is required to reduce the incidence of perinatal maternal-infant complications. We have demonstrated that hemoglobin A1c does not reflect glycemic control accurately during pregnancy because of iron deficiency. On the other hand, glycated albumin is not influenced by iron deficiency and therefore might be a better indicator of glycemic control in patients with GDM and pregnant women with diabetes. However,

large-population epidemiological studies are necessary. Here, we outline the most recent findings about the indicators of glycemic control during pregnancy including fructosamine and 1,5-anhydroglucitol.

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INTRODUCTION

The number of patients with diabetes mellitus has been steadily increasing worldwide[1] and diabetes mellitus has become a global health problem. This tendency is also observed in women of child-bearing age partly due to the change in diagnostic criteria of gestational diabetes mellitus (GDM) as mentioned later. The incidence of GDM in Japan has increased by 4.1 fold from 2.9% to 12.1%[2]. By detecting abnormal maternal glucose metabolism at an early stage of pregnancy and achieving excellent glycemic control during pregnancy, it is possible to prevent perinatal maternal-infant complications[3,4]. According to a report on a meta-analysis of 20 studies, the relative risk for patients with GDM of developing type 2 diabetes mellitus after delivery is 7.43 times higher than that of women who had normal glucose tolerance during pregnancy[5]. Therefore, it is important to follow up mothers after delivery. Moreover, the concept of developmental origins of health and diseases was proposed recently[6] and the long-term effects of mothers with abnormal glucose tolerance on fetuses after birth have been actively discussed. Thus, it is important to manage glycemic control of mothers appropriately not only because it helps to maintain the health of mothers and infants in the short term, but also helps to maintain the long-term health of mothers and the next generation. In the following sections, we outline the management of pregnant women with abnormal glucose metabolism. Finally, we propose a reliable indicator of glycemic control.

CHANGES IN GLUCOSE METABOLISM DURING PREGNANCY

During the early stage of pregnancy, increased secretion of progesterone and 17β-estrogen from the corpus luteum is observed; after the placenta is completed, it replaces the role of the corpus luteum. In humans, it is known that during pregnancy, the secretion of estrogen increases by about 30 fold and that of progesterone by about 10 fold compared with that during non-pregnancy. In addition, the secretion of prolactin and placental lactogen also increases gradually from week 12 of pregnancy. Placental lactogen is considered to be one of the typical hormones involved in the change in insulin sensitivity during pregnancy. Moreover, it has been shown that tumor necrosis factor-α secreted from macrophages which infiltrate into fat cells and villous cells is deeply involved in decreased insulin sensitivity[7]. It is known that high concentrations of estrogen and progesterone also induce decreased insulin sensitivity[8,9]. Because of the involvement of hormones and cytokines as mentioned above, there is a substantial change in glucose metabolism during pregnancy. In clinical researches conducted by Catalano *et al*[10-12], increased gluconeogenesis in the liver during the end stage of pregnancy demonstrated decreased insulin sensitivity in the liver. In addition, it has been shown that systemic insulin sensitivity decreases by about 50% to 60% during the end stage of pregnancy[13]. In pancreatic β-cells, increased β-cell volume and increased insulin secretion reaction take place to compensate for their insulin resistance. Regarding the mechanism of this phenomenon, it has been reported that serotonin is present downstream of the prolactin signal, which promotes pancreatic β-cell growth and greatly contributes to an increase in the cell volume[14]. It is considered that abnormal glucose tolerance develops in pregnant women when this compensatory effect is insufficient. In fact, the presence of pancreatic β-cell dysfunction in GDM has been demonstrated[15,16].

DEFINITION OF GDM

GDM, which was found or developed for the first time during pregnancy, is milder abnormal glucose metabolism than diabetes mellitus. It should be noted that GDM does not include overt diabetes in pregnancy[17].

It is not appropriate to apply the diagnostic criteria of diabetes mellitus during non-pregnancy as the diagnostic criteria of abnormal glucose tolerance during pregnancy for the following reasons. Firstly, the altered hormonal environment and the presence of the fetus during pregnancy cease at the time of delivery. Secondly, the diagnostic criteria of diabetes mellitus during non-pregnancy are established based on the incidence of diabetic complications (especially, diabetic retinopathy); on the other hand, the diagnostic criteria of GDM are established for the prevention of diabetes mellitus of mothers and the prevention of perinatal complications of mothers and infants. The diagnostic criteria of GDM of each country that were used in the past were established to prevent future onset of diabetes mellitus, and differed among countries. These differences in the definition of GDM caused various problems in international discussions. Accordingly, the International Association of Diabetes and Pregnancy Study Groups announced worldwide uniform diagnostic criteria of GDM[17] based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study[18] reported in 2008 (Table 1). The HAPO study was conducted in 25505 pregnant women at 15 facilities in nine countries worldwide to evaluate outcomes of mothers and infants; the data of the partici-

Table 1 To diagnose gestational diabetes mellitus and cumulative proportion of Hyperglycemia and Adverse Pregnancy Outcome cohort equaling or exceeding those thresholds

Glucose measure	Glucose concentration threshold[1]		Above threshold (%)
	mmol/L	mg/dL	cumulative
FPG	5.1	92	8.3
1-h plasma glucose	10.0	180	14.0
2-h plasma glucose	8.5	153	16.1[2]

[1]One or more of these values from a 75-g OGTT must be equaled or exceeded for the diagnosis of GDM; [2]In addition, 1.7% of participants in the initial cohort were unblinded because of FPG > 5.8 mmol/L (105 mg/dL) or 2-h OGTT values > 11.1 mmol/L (200 mg/dL), bringing the total to 17.8% (modified from Ref.[17]). FPG: Fasting plasma glucose; OGTT: Oral glucose tolerance test.

pants were opened to the primary physician only when fasting plasma glucose was not less than 105 mg/dL or plasma glucose at 2 h after meal was not less than 200 mg/dL; otherwise, the data were blinded to the primary physician. Primary outcomes included birth weight of not less than the 90 percentile, percentage of cesarean section, neonatal hypoglycemia, and cord serum C-peptide of not less than the 90 percentile; secondary outcomes included premature labor, shoulder dystocia/dystocia, hyperbilirubinemia, neonatal intensive care unit management, and pregnancy-induced hypertension syndrome. As a result, there was no threshold at which the incidence of primary outcomes showed a clear increase; plasma glucose level, whose odds ratio is 1.75 times higher than that in the lowest category, was adopted as the diagnostic cut-off value[17]. Regarding glycemic control indicators, there were no clear diagnostic threshold. Thus, the shift from the diagnostic criteria of GDM based on the future incidence of diabetes mellitus of mothers to diagnostic criteria of GDM for improving perinatal outcomes of mothers and infants during pregnancy was a major event.

ADVERSE EVENTS DURING PREGNANCY OF GDM AND OVERT DIABETES MELLITUS

Because the definition of GDM is based on the incidence of perinatal complications of mothers and infants, we give an outline of perinatal complications once again. Maternal complications include pregnancy-induced hypertension syndrome, polyhydramnios, shoulder dystocia, and cesarean section. In pregnant women with diabetes mellitus, careful attention should also be paid to diabetic ketoacidosis, worsening of diabetic retinopathy and diabetic nephropathy, and hypoglycemia. For pregnancy-induced hypertension syndrome, 2% to 8% of all pregnant women are complicated with preeclampsia, which worsens perinatal outcomes. The late-onset form, which accounts for 80% of all cases of pregnancy-induced hypertension syndrome, is of maternal origin and is often accompanied by old age, obesity, diabetes mellitus, and chronic hypertension. That is to say, it is considered that abnormal glucose metabolism of mothers influences the onset of pregnancy-induced hypertension syndrome. Next, it has been reported that 0.5% to 0.7% of normal pregnant women and 2.0% to 2.1% of patients with GDM are complicated with polyhydramnios[19,20]. Polyhydramnios induces complications leading to perinatal death including premature labor, premature rupture of membranes, fetal malpresentation, weak labor, umbilical cord prolapse, premature separation of normally implanted placenta, and atonic hemorrhage after delivery. For pregnant women with diabetes mellitus, it has been reported that glucose concentration in amniotic fluid is related to maternal plasma glucose level[21] and that there is a positive correlation between amniotic fluid volume and glucose concentration in amniotic fluid[22]. Shoulder dystocia is a condition in which after the head of the infant is delivered in cephalic vaginal delivery, the shoulder of the infant is not delivered. It is a disease which may cause dystocia in both the mother and the infant. It is known that macrosomia is a risk factor for shoulder dystocia; on the other hand, it has been reported that pregnant women with abnormal glucose tolerance tend to experience shoulder dystocia regardless of the presence or absence of macrosomia[23]. For these reasons and also because of complications of fetuses as mentioned later, the percentage of cesarean section is obviously higher in pregnant women with abnormal glucose tolerance; the percentage is 10.7%-18.9% in normal pregnant women, compared with 19.3%-30.9% in pregnant women with GDM and 45.2% in pregnant women with diabetes mellitus[20,24-27].

Congenital anomaly is one of the complications of fetuses born from mothers with diabetes mellitus. According to a report in Japan, the incidence of congenital anomaly does not increase obviously when hemoglobin A1c (HbA1c) during the early stage of pregnancy is less than 7.4%; however, the incidence increases when HbA1c is 7.4% or more; the incidence is as high as 24.1% when HbA1c is 8.4% or more[28]. Macrosomia as a developmental anomaly is a fetal developmental anomaly unique to pregnancy in women with diabetes mellitus. The hyperglycemia-hyperinsulinemia hypothesis proposed by Pedersen[29] is that hyperglycemia of mothers induces hyperglycemia of fetuses, and hyperplasia of pancreatic β-cells of fetuses results in hypersecretion of insulin, leading to excessive growth of fetuses. Infants

born from mothers with diabetes mellitus are called infants of diabetic mothers and are known as high-risk infants in whom multiple complications develop at a high incidence[30]. Such complications include hypoglycemia, polycythemia, hyperbilirubinemia, hypocalcemia, neonatal respiratory distress syndrome, and myocardial hypertrophy.

TREATMENT OF PREGNANT WOMEN WITH GDM AND OVERT DIABETIC MELLITUS

The basis of plasma glucose management during pregnancy is dietary therapy similar to that during non-pregnancy. As nutrition for fetuses during pregnancy, glucose, amino acids, and free fatty acids are supplied through the maternal placenta; the main energy source for fetuses is glucose. The main points of dietary therapy for pregnant women with abnormal glucose tolerance are to prevent ketosis of mothers resulting from insufficient carbohydrate intake and to perform strict glycemic control. In other words, energy intake at which the body weight of mothers before pregnancy does not decrease is determined as the basic food intake, and energy for fetuses according to the stage of pregnancy is added to it.

If the goal of glycemic control is not achieved in spite of dietary therapy, insulin therapy is selected. Currently, the types of insulin that can be used safely during pregnancy are human insulin as well as insulin aspart, insulin lispro, and insulin detemir; they are classified into the United States Food and Drug Administration (FDA) Pregnancy Category B. Insulin glargine and insulin glulisine are currently classified into the FDA Pregnancy Category C, and their potential risk cannot be ruled out. The principle of insulin therapy during pregnancy, which consists of supplementation of basal insulin secretion and supplementation of additional insulin secretion at the time of dietary intake, is the same as that during non-pregnancy. It should be noted that during the early stage of pregnancy, the insulin requirement decreases because of hyperemesis gravidarum, *etc.*; during and after the middle stage of pregnancy, insulin resistance increases; during the end stage of pregnancy, the insulin requirement increases to about two times that before pregnancy.

MEASUREMENT OF BLOOD GLUCOSE

In order to prevent perinatal complications of mothers and infants mentioned above, the goal of glycemic control during pregnancy should be to bring plasma glucose level as close to normal as possible without development of hypoglycemia. Strict glycemic control should be performed by self-monitoring of plasma glucose (SMBG) or continuous glucose monitoring (CGM).

SMBG

SMBG enables strict glycemic control. To achieve this, it is important to make patients understand why blood glucose should be measured, and to remind patients of the relationship between activity, events, meals, snacks, etc. and blood glucose levels. Because pregnant women tend to become anemic easily, this tendency should be taken into consideration. When hematocrit is low, plasma volume increases and plasma glucose level increases; conversely, when hematocrit is high, plasma volume decreases and plasma glucose level decreases. If insulin therapy is being performed, the insulin dose for glycemic control is adjusted based on the result of SMBG. The basic principle is to adjust basal insulin dose according to fasting blood glucose level and to adjust additional insulin dose according to postprandial blood glucose level. Langer *et al*[31] have reported that when fasting blood glucose is not less than 95 mg/dL in patients with GDM, the incidence of macrosomia significantly increases, and the incidence is decreased by insulin therapy. In addition, they have demonstrated that it is possible to decrease the incidence of both small-for-gestational-age and large-for-gestational-age by bringing mean blood glucose level to 87-104 mg/dL[32]. On the other hand, it has been reported that adjusting insulin therapy according to postprandial blood glucose level results in an improvement of glycemic control, a decrease in neonatal hypoglycemia, a decrease in macrosomia, and a decrease in cesarean section[33].

CGM

The CGM device can monitor blood glucose level every 5 min for up to 7 d. The device has demonstrated that there is a difference in circadian rhythm of blood glucose among non-diabetic pregnant women between normal-weight pregnant women and obese pregnant women[34]. That is, compared with normal-weight pregnant women, obese pregnant women have comparable fasting blood glucose and comparable mean blood glucose but higher postprandial blood glucose and lower nighttime blood glucose. Compared with SMBG, the CGM device can monitor glycemic excursion in greater detail, but continuous wearing of the device is neither economically viable nor suitable for continuous evaluation. However, the CGM device is a useful education tool for pregnant women with diabetes mellitus, and it has been reported that by performing CGM every 4 to 6 wk during pregnancy, glycemic control during the third trimester of pregnancy improved, and the risk of macrosomia decreased[35]. In addition, the ability to identify hypoglycemia is another noteworthy benefit of CGM. Rosenn *et al*[36] have demonstrated by CGM that 30% of pregnant women with type 1 diabetes mellitus experience at least three episodes of hypoglycemia during 2 wk. In such patients, it is possible to perform safer and more appropriate insulin therapy by performing CGM.

INDICATORS OF GLYCEMIC CONTROL

Plasma glucose measurement is important as part of glycemic control during pregnancy; however, it is actually difficult to measure blood glucose in all patients. Therefore, it is necessary to evaluate glycemic control condition using indicators of glycemic control such as HbA1c, glycated albumin (GA), fructosamine, and 1,5-AG. Each of these indicators of glycemic control has different characteristics as well as advantages and disadvantages[37,38]. In addition, there are both appropriate and inappropriate indicators of glycemic control during pregnancy. The following sections give an outline of these indicators of glycemic control.

HbA1c

HbA1c is a ketoamine formed from nonenzymatic reaction and binding between the aldehyde group of glucose and valine at the N-terminus of the hemoglobin β-chain. Because the life span of red blood cells is 120 d, HbA1c reflects glycemic control status during the past 1 to 2 mo. Specifically, the following findings have been reported: 50% reflect plasma glucose level during the past 1 mo; 25% reflect plasma glucose level during the past 1 to 2 mo; 25% reflect plasma glucose level during the past 2 to 4 mo[39]. Since the Diabetes Control and Complications Trial study[40], extensive evidence on the development and progress of complications has been gathered, and HbA1c has certainly become a gold standard indicator of glycemic control. Therefore, it is recommended to maintain excellent glycemic control in pregnant women with diabetes mellitus or patients with GDM using SMBG and HbA1c as indicators[41]. However, pregnant women are usually excluded from clinical studies of complications, and therefore little evidence has been obtained from pregnant women. Because chronic diabetic complications usually do not develop within a period as short as several months, there is no problem in using HbA1c as an indicator; however, there is little benefit in discussing glycemic control status during the past 1 to 2 mo of pregnancy. In addition, it is well known that HbA1c is influenced by the life span of red blood cells. Moreover, we have reported that for premenopausal women, HbA1c is significantly higher not only in women with iron deficiency anemia but also in women with iron deficiency compared with HbA1c in women without iron deficiency[42,43]. It is well known that the demand for iron increases during the end stage of pregnancy and that most mothers experience iron deficiency anemia; therefore, HbA1c may be higher relative to plasma glucose level during the end stage of pregnancy. The time course of HbA1c during pregnancy will be explained in detail later.

Fructosamine

Protein undergoes glycation reaction in accordance with plasma glucose concentration, and ketoamine, an early Maillard reaction product, is produced *via* aldimine. Because the side chain binding of ketoamine has the fructose structure, ketoamine is generically named fructosamine. Fructose-lysine (fructosamine), in which glucose is bound to lysine residue of protein, has a reducing ability under alkaline conditions; glycemic control is measured using this reducing ability. A large part of such measurement is made by the fructosamine method; glycemic control is measured by colorimetric determination by producing reduction color reaction using nitroblue tetrazolium as a substrate. Because 60% to 70% of serum protein is albumin, the main component of fructosamine is GA, but fructosamine contains other components such as glycated lipoprotein and glycation globulin. Fructosamine is not influenced by anemia or abnormal hemoglobin. In addition, albumin, which accounts for the majority of serum protein, has a faster turnover than hemoglobin; therefore, short-term glycemic control can be evaluated by measuring fructosamine[44]. In hyperthyroidism[45,46] and nephrotic syndrome[47] in which protein (albumin) metabolism is increased, fructosamine measured by this method is low; in hypothyroidism[45] in which protein (albumin) metabolism is delayed, fructosamine measured by this method is high.

HbA1c is a glycation product of hemoglobin (single protein) and GA is a glycation product of albumin (single protein); on the other hand, fructosamine is the generic name of all glycated proteins and lacks specificity. Because 60% to 70% of serum protein is albumin, the characteristics of fructosamine are similar to those of GA. However, this method measures other glycated proteins as well; therefore, there is a problem that in myeloma, fructosamine measured by this method is high[48]. In addition, it has been reported that fructosamine is associated with a larger intra-individual variability compared with HbA1c, and fructosamine is disadvantageous for detecting a significant change[49]. HbA1c is expressed as the ratio of hemoglobin and GA is expressed as the ratio of albumin; therefore, HbA1c and GA are not influenced by dilution of serum. On the other hand, fructosamine is expressed as reducing ability per 1 mL of serum; therefore, fructosamine is influenced by serum protein concentration, and in dilutional anemia, fructosamine measured by this method is apparently low. In this respect, fructosamine measured by this method is likely to be influenced by dilutional anemia which may develop during pregnancy. Because fructosamine is measured by colorimetric determination produced by reduction color reaction, it is influenced by substances with reducing ability such as bilirubin. It is considered that the effects of ascorbic acid and vitamin E are small; however, if they are consumed in large amounts, measurement of fructosamine may be influenced.

GA

GA is a ketoamine formed from nonenzymatic reaction and binding between four lysine residues of albumin and glucose. In other words, GA is an amadori compound similar to HbA1c, but it has been reported that the binding rate between albumin and glucose is 4.5 times higher than that between hemoglobin and glucose[50]. Because the half-life of albumin is about 14 d, GA is

an indicator of glycemic control during a shorter period (during the past 2 to 3 wk) compared with HbA1c. In addition, it is known that GA reflects postprandial plasma glucose more accurately than HbA1c[37]. In the management of abnormal glucose metabolism during pregnancy, evaluation of mean plasma glucose level at a time point closer to the time of consultation with a doctor and evaluation of postprandial plasma glucose level are important, and GA is useful in this respect. Moreover, we have already reported that GA is not influenced by iron deficiency anemia or iron deficiency state[43]. It should be noted that because GA is influenced by albumin metabolism, evaluation of measured GA levels requires attention in conditions such as nephrotic syndrome[51] and abnormal thyroid function[52]. Unlike fructosamine, GA is not influenced by dilutional anemia during pregnancy. The time course of GA during pregnancy will be explained in detail later.

1,5-AG

1,5-AG is a polyol with a structure in which hydroxyl at the first position of glucose is reduced; it is contained in a wide variety of food, but is hardly metabolized in the body[53]. When plasma glucose is within the normal range, 1,5-AG is filtered in the kidney and then reabsorbed completely; therefore, serum 1,5-AG remains unchanged.

Usually, about 180 g of glucose is excreted from glomeruli daily, but almost 100% of the excreted glucose is reabsorbed by sodium glucose cotransporter 2 (SGLT2) which is a glucose-specific transporter and located in proximal tubules and SGLT1 which is a transporter for glucose and galactose and located downstream of SGLT2[54]. When diabetes mellitus develops, excretion of glucose increases; if excretion of glucose exceeds the reabsorptive capacity of SGLT2 and SGLT1, reabsorption of glucose by 1,5-AG/mannose/fructose cotransporter (sodium glucose cotransporter 4: SGLT4) which is present downstream from SGLT2 and SGLT1 takes place. Usually, there is no glucose in locations where SGLT4 is present; therefore, 99.9% of 1,5-AG is reabsorbed by SGLT4; however, because SGLT4 reabsorbs glucose as well, if the inflow of glucose into tubules increases, reabsorption of 1,5-AG is inhibited[55-57]. Specifically, if plasma glucose level exceeds 180 mg/dL, glucose is excreted in urine; therefore, 1,5-AG is also excreted in urine and serum 1,5-AG decreases.

Because of this mechanism, serum 1,5-AG reflects glycemic status during the past 24 h and is used as an indicator of very short-term glycemic control[58,59]. In addition, serum 1,5-AG is an indicator which reflects postprandial hyperglycemia more accurately than HbA1c[60,61]. It should be noted that in patients with marked hyperglycemia and a large urinary glucose excretion, even if glycemic control improves, serum 1,5-AG does not increase in a short period because the 1,5-AG pool in the body has decreased.

Because serum 1,5-AG is influenced by the threshold for urinary glucose excretion as well, serum 1,5-AG is low in renal glycosuria in which the threshold decreases. In chronic renal failure[62-64] in which reabsorption of 1,5-AG decreases, 1,5-AG is low because of transient glucosuria. In other conditions such as oxyhyperglycemia[65], patients receiving long-term hyperalimentation[66], and liver cirrhosis[67,68], serum 1,5-AG is abnormally low. On the other hand, one of the causes of abnormally high 1,5-AG levels is oral administration of Ninjin-yoei-to and Kami-kihi-to[69] which contain a large amount of 1,5-AG.

It has been reported that because the threshold for glucose in the kidney decreases during pregnancy, glucose tolerance may not change, and glucosuria may appear[70]. It has also been reported that serum 1,5-AG during pregnancy is low because of this mechanism[71]. Therefore, serum 1,5-AG during pregnancy does not reflect glycemic control accurately and is not an appropriate indicator of glycemic control.

CHANGE IN INDICATORS OF GLYCEMIC CONTROL DURING PREGNANCY

Change in indicators of glycemic control during normal pregnancy

In the past, Phelps *et al*[72] reported the time course of HbA1c during pregnancy in 377 non-diabetic pregnant women and the time course of plasma glucose level at 1 h after 50 g oral glucose loading in 1756 normal pregnant women. It was demonstrated that HbA1c shows a biphasic change with the trough level occurring at week 24 of pregnancy and that 1 h plasma glucose level also shows a biphasic change with the trough level occurring at week 20 of pregnancy. In a report of the Japanese Society of Diabetes and Pregnancy[73], similar tendencies were shown; according to an analysis of 574 normal pregnant women, HbA1c tends to decrease during the middle stage of pregnancy and increase during the end stage of pregnancy, and GA tends to decrease gradually toward the end stage of pregnancy (Figure 1). Judging from this report, the reference range in Japanese normal pregnant women was considered to be 4.4% to 5.7% for HbA1c and 11.5% to 15.7% for GA. In any case, there is undoubtedly a difference between the time course of HbA1c and GA during pregnancy, so which indicator of glycemic control is reliable? We investigated the effect of iron deficiency on HbA1c in 17 normal pregnant women[74]. HbA1c increased significantly from the middle stage of pregnancy (wk: 20-23) to the end stage of pregnancy (wk: 32-33) (4.7% ± 0.2% *vs* 5.1% ± 0.2%; $P < 0.0001$). On the other hand, GA showed no significant change. Mean corpuscular hemoglobin (MCH), transferrin saturation, and serum ferritin, which are indicators of iron deficiency, showed a decrease toward the end stage of pregnancy; there was a significant negative correlation between HbA1c and MCH, transferrin saturation, and serum ferritin (Figure 2). On the other hand, there was no significant correlation between GA and MCH, transferrin saturation, and serum ferritin. Based on the above findings, it is considered that in normal pregnant women, iron deficiency progresses during the end stage of pregnancy, and therefore HbA1c

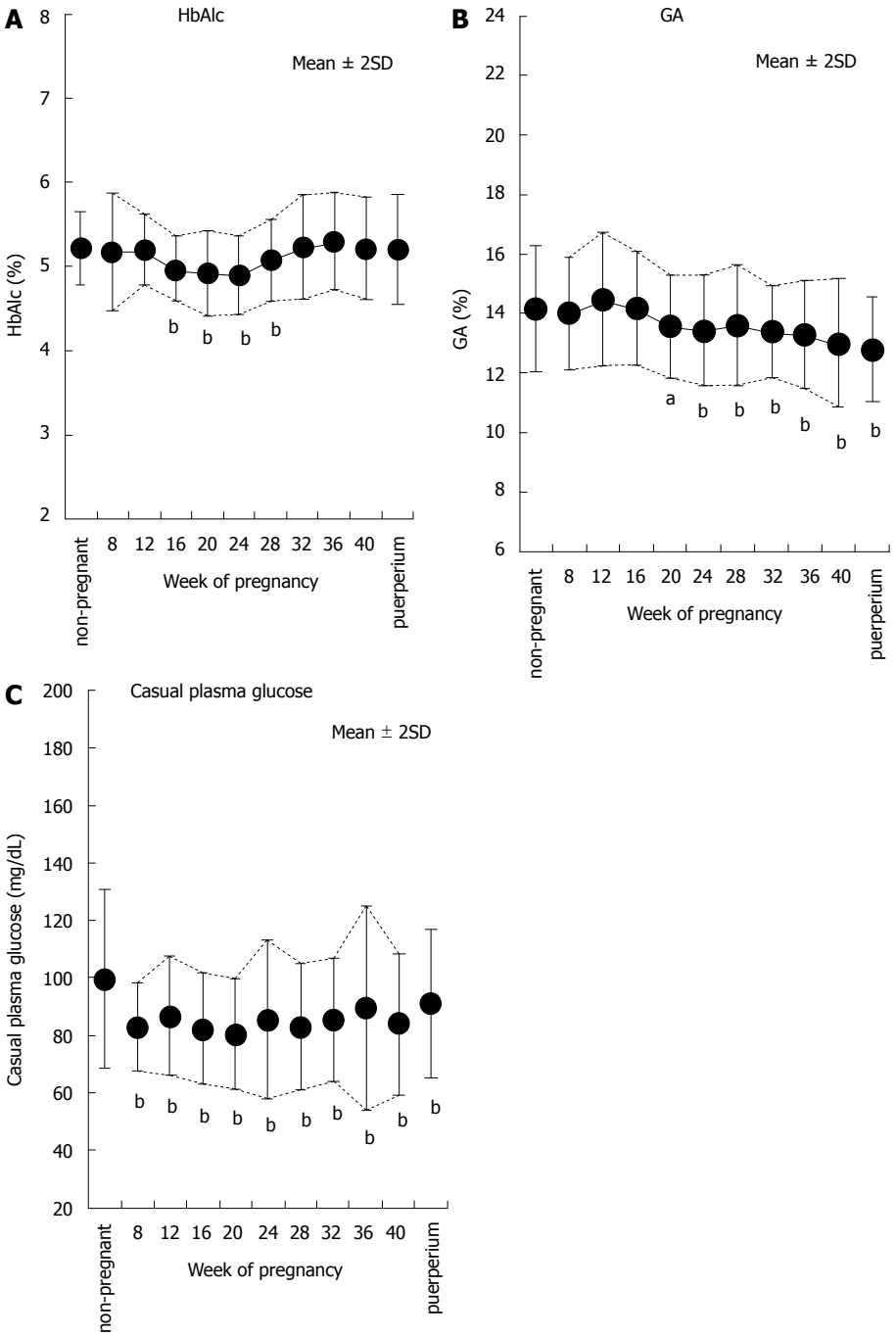

Figure 1 Time courses of indicators of glycemic control in normal pregnant women. The time courses of HbA1c (A), GA (B), and casual plasma glucose (C) in normal pregnant women are shown (modified from Ref.[73]). $^{a}P < 0.05$, $^{b}P < 0.01$ *vs* non-pregnant women. HbA1c: Hemoglobin A1c; GA: Glycated albumin.

level increases. That is, HbA1c during pregnancy may not be a reliable indicator of glycemic control, especially during the end stage of pregnancy. However, if pregnant women take in a sufficient amount of iron during pregnancy, increase of HbA1c may not occur from the middle stage to the end stage of pregnancy as shown in Figure 1.

Change in indicators of glycemic control of women with GDM and overt diabetes mellitus

Glycemic control status is important in pregnant women with diabetes mellitus and patients with GDM. For the time courses of HbA1c and GA in pregnant women with diabetes mellitus and patients with GDM as well, the GA Study Group of the Japanese Society of Diabetes and Pregnancy has issued a detailed report[75]. According to this report, in 193 pregnant women with diabetes mellitus and patients with GDM, HbA1c decreased during the middle stage of pregnancy and then increased during the end stage of pregnancy, as in the case of normal pregnant women. On the other hand, GA decreased as the gestational age advanced (Figure 3). However, gestational diabetes was not distinguished from pregnancy complicated with preexisting diabetes in this report. The time courses of HbA1c and GA were similar to

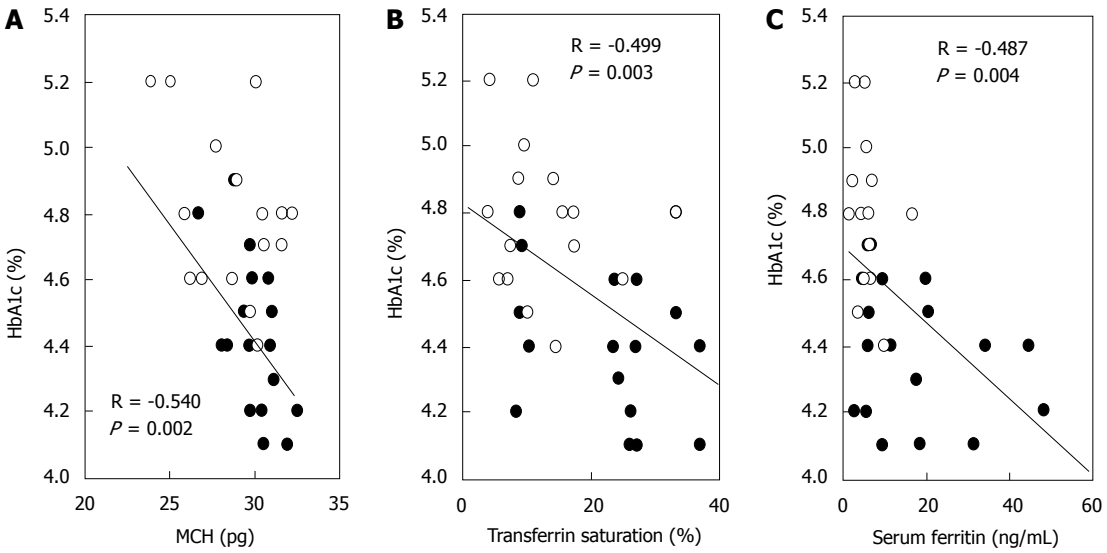

Figure 2 Correlations between hemoglobin A1c and indicators of iron deficiency in normal pregnant women. The correlations between HbA1c and mean corpuscular hemoglobin (MCH) (A), transferrin saturation (B), and serum ferritin (C) in normal pregnant women are shown (modified from Reference[74]). ●: Middle stage of pregnancy (wk: 20-23); ○: End stage of pregnancy (wk: 32-33); HbA1c: Hemoglobin A1c.

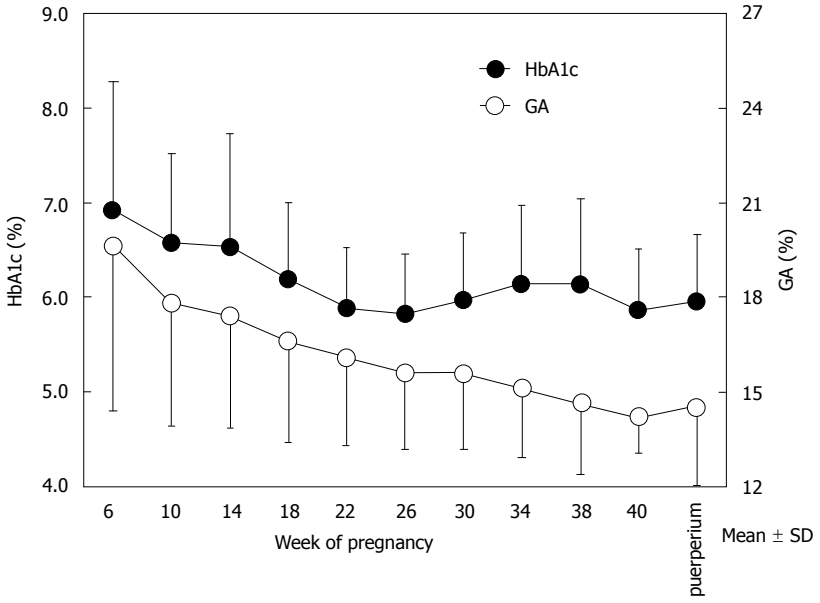

Figure 3 Time courses of hemoglobin A1c and glycated albumin in pregnant women with diabetes mellitus and patients with gestational diabetes mellitus. The time courses of HbA1c (closed circles) and GA (open circles) in pregnant women with diabetes mellitus and patients with gestational diabetes mellitus are shown (modified from Hiramatsu *et al*[73]). HbA1c: Hemoglobin A1c. GA: Glycated albumin.

those observed in normal pregnant women; as expected, there was a difference between time courses of different indicators of glycemic control. Therefore, we made a similar investigation in 11 pregnant women with diabetes mellitus (7 patients with type 1 diabetes mellitus and 4 patients with type 2 diabetes mellitus) and 6 patients with GDM[76]. As in the case of normal pregnant women, HbA1c increased significantly from the middle stage of pregnancy (wk: 20-23) to the end stage of pregnancy (wk: 32-35) (5.8% ± 0.7% *vs* 6.1% ± 0.6%; $P < 0.05$), whereas GA showed no significant change. During the end stage of pregnancy, MCH, transferrin saturation, and serum ferritin level decreased, and there was a significant positive correlation between transferrin saturation and the GA/HbA1c ratio. These results show that in pregnant women with diabetes mellitus and patients with GDM, iron deficiency progresses, and HbA1c increases during the end stage of pregnancy.

We introduce a typical pregnant woman with diabetes mellitus (36-year-old woman) as one of our patients. She was not obese before pregnancy (BMI before pregnancy was 22.7 kg/m^2) and treatment with insulin therapy was started before pregnancy. As the gestational age advanced, HbA1c increased from 6.2% (wk 18) to

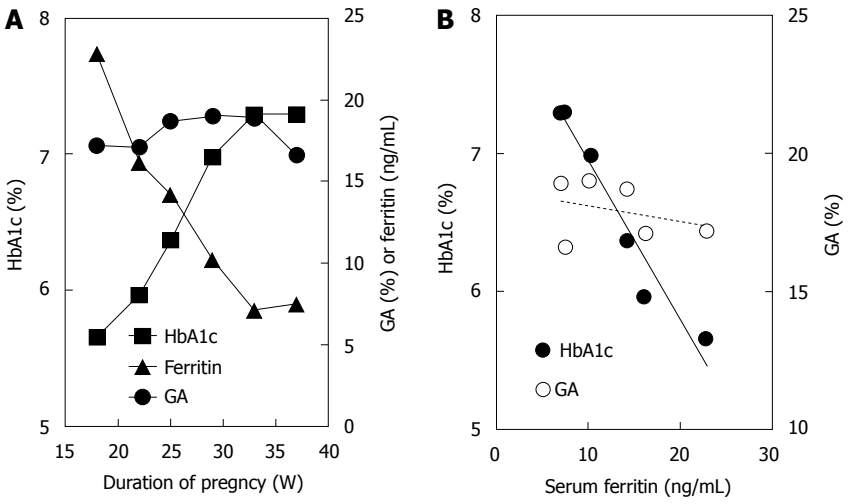

Figure 4 Time courses of hemoglobin A1c and glycated albumin and correlations between serum ferritin and hemoglobin A1c or glycated albumin in a pregnant woman with diabetes mellitus. A: The time courses of HbA1c (closed squares), GA (closed circles), and serum ferritin (closed triangles) in a pregnant woman with diabetes mellitus (a 36-year-old woman with type 2 diabetes mellitus receiving insulin therapy), are shown; B: Correlations between serum ferritin and HbA1c (R = -0.975, $P < 0.001$) or GA (R = 0.322, $P = 0.534$) in a pregnant woman with diabetes mellitus are shown. HbA1c: Hemoglobin A1c; GA: Glycated albumin.

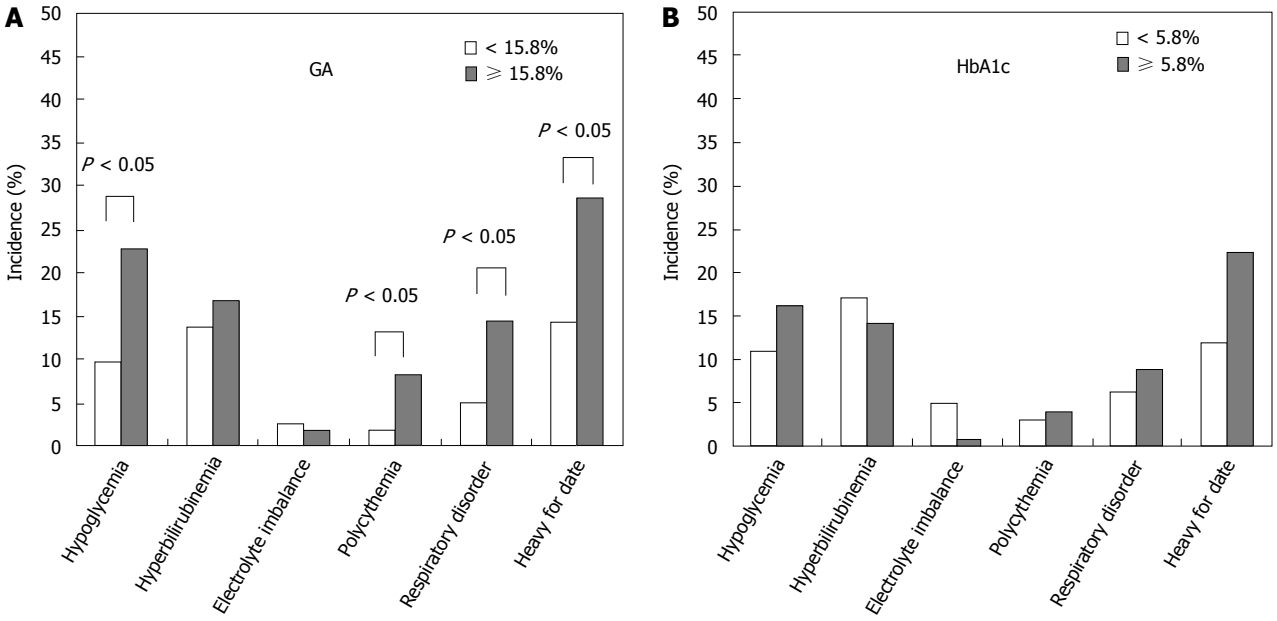

Figure 5 Comparison between glycated albumin and hemoglobin A1c during pregnancy and the incidence of neonatal complications. For GA (A) and HbA1c (B) measured during the end stage of pregnancy, the incidence of neonatal complications was compared between the group of women whose GA or HbA1c was within the reference range (GA < 15.8%; HbA1c < 5.8%) and the group of women whose GA or HbA1c exceeded the reference range (GA ⩾ 15.8%; HbA1c ⩾ 5.8%) (modified from Shimizu *et al*[75]). HbA1c: Hemoglobin A1c; GA: Glycated albumin.

7.3% (wk 37), which suggested worsening of glycemic control status. However, GA was stable between 17.2% (wk 18) and 16.6% (wk 37). In contrast, serum ferritin decreased from 22.8 ng/mL (wk 18) to 7.5 ng/mL (wk 37) during this period (Figure 4A). Because the time course of HbA1c and serum ferritin formed a mirror image, it was considered that the increase in HbA1c during the end stage of pregnancy was not due to poor glycemic control status but due to iron deficiency anemia (iron deficiency state). We emphasize that HbA1c (R = -0.935, $P < 0.001$), but not GA (R = 0.322, $P = 0.534$), was negatively correlated with serum ferritin (Figure 4B). In conclusion, GA is not influenced by iron deficiency and so is a reliable indicator of glycemic control.

ASSOCIATION BETWEEN INDICATORS OF GLYCEMIC CONTROL AND COMPLICATIONS IN THE PERINATAL PERIOD

The GA Study Group of the Japanese Society of Diabetes and Pregnancy has analyzed the association between outcomes (neonatal complications and birth weight)

and indicators of glycemic control (HbA1c and GA)[75]. The analysis was made considering the upper limits in normal pregnant women (HbA1c: 5.7%; GA: 15.7%); for neonatal complications, the incidences of neonatal hypoglycemia, polycythemia, and respiratory disorder were found to be significantly higher in the group of women with GA of more than 15.7% (Figure 5). In addition, it was reported that the incidence of large-for gestational age was also significantly higher in the group of women with GA of more than 15.7% compared with the group of women with GA of 15.7% or less. On the other hand, it was reported that there was no significant increase in the incidence in the group of women with HbA1c of more than 5.7% compared with the group of women with HbA1c of 5.7% or less. Although a more accurate judgment should be made by ROC analysis for different cut-offs, GA is superior to HbA1c for prediction of perinatal complications. Furthermore, appropriate regression analysis is necessary to see if the indicator remains significant after eliminating the iron factors. As we demonstrated in our patients, if HbA1c is apparently high during the end stage of pregnancy, it may be misinterpreted that glycemic control has worsened and excessive insulin therapy may be performed, leading to hypoglycemia and increased incidence of perinatal complications of mothers and infants. Hence, management based on GA is essential during pregnancy also from the viewpoint of perinatal complications.

CONCLUSION

We outlined indicators of glycemic control in abnormal glucose metabolism during pregnancy. As explained, it is insufficient during pregnancy to use HbA1c as an indicator of glycemic control; glycemic control using GA is recommended. It is necessary to measure HbA1c to enable comparison with the large amount of data accumulated so far; the goal of management of abnormal glucose metabolism during pregnancy might be to maintain GA within the normal range (15.7% or less). However, because little data from clinical studies is available, large-population epidemiological studies would be necessary in order to confirm our proposal.

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REVIEW

Is there a relationship between vitamin D with insulin resistance and diabetes mellitus?

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Abstract

Available data suggest a possible link between abnormal vitamin D level and abnormal glucose homeostasis, two of the most common chronic medical conditions. Both conditions are associated with inflammation, and the exact mechanism for role of either on the other is not well clear. Literature investigating the link between vitamin D and either pre-diabetic states or diabetes is reviewed. Vitamin D deficiency is detrimental to insulin synthesis and secretion in animal and human studies. In humans, it has been shown by majority of observational studies, that vitamin D is positively correlated with insulin sensitivity and its role is mediated both by direct mechanism through the availability of vitamin D receptors in several tissues and indirectly through the changes in calcium levels. Large number of, but not all, variable samples cross sectional human trials have demonstrated an inverse relation between vitamin D status and impaired glucose tolerance, insulin resistance or diabetes. To compliment this conclusively, evidence from intervention studies is critically warranted before we can frankly state that vitamin D plays a role in diabetes prevention or treatment. Absence of both sizable prospective observational trials utilizing 25(OH)D as the main variable and the non-availability of randomized studies specifically designed to assess the effects of vitamin D on pre-diabetes and diabetes states, are the main obstacles to draw solid and conclusive relationships.

Key words: Vitamin D; Insulin resistance; Type 2 diabetes

Core tip: A potential role for abnormal vitamin D level in changes of glucose homeostasis has been described. It has been demonstrated that deficient vitamin D status is detrimental to the synthesis and secretion of insulin in animal and human studies. In several, but not all, human observational trials, an inverse correlation was seen between vitamin D with insulin insensitivity, pre-diabetic states and dysglycemia. However, evidence from randomized interventional studies assessing the

effects of changes in vitamin D status on markers of dysglycemia and diabetes prevention is not available. Therefore, firm and true protective influence of vitamin D on glucose homeostasis remains to be defined.

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INTRODUCTION

The widely common medical conditions, low vitamin D level and diabetes with its proceeding pre-diabetic state of insulin resistance, have become two of the most common chronic medical conditions diagnosed in modern years, both in developing and developed countries. There are around 387 million diabetic patients worldwide in year of 2014 and that number is projected to increase by 55% in 2035, as Africa is the highest projected region to have increased prevalence followed by the Middle East. The prevalence of impaired glucose tolerance, or insulin resistance, is even higher. Diabetes is leader in causing cardiovascular diseases and was responsible for 5.1 million deaths last year only[1].

Vitamin D deficiency is now recognized as a pandemic. Its prevalence varies according to geographic location, season, ethnicity and the standard laboratory value of what is considered normal, deficient and insufficient vitamin D. It was estimated that there were about 1 billion individuals with low vitamin D in 2008 and the number most likely is higher now[2]. Well-studied adverse outcomes of vitamin D deficiency are low bone density[3], non-vertebral fractures[4], increased risk of hip fracture[5] and slowed walking speed[6].

The link of vitamin D with insulin insensitivity or abnormal glucose metabolism gained much more scientific attention in the last decade. Several observations or associations were cited exploring the possible role for either altered vitamin D status and its metabolites or altered insulin sensitivity in the pathogenesis of the each disease. To gain more insight on the role of these variables, understanding of the metabolism of vitamin D and its relation to the pancreas is crucial.

VITAMIN D METABOLISM

In humans, vitamin D3 is mostly obtained from endogenous vitamin D resources as a result of skin exposure to ultraviolet B light and only a minor portion is extracted from meals containing fortified milk and dairy food resources, eggs, and wild oily sea fish[7] (Figure 1). It is crucial to note that vitamin D2 is the non-animal plant derived form of vitamin D and is called ergosterol. Vitamin D3 is a lipophilic precedent of the major circulating 25(OH) D3 metabolite which is hydroxylated, predominantly in the kidney, by a single enzyme 1 α-hydroxylase [1α(OH)lase; CYP27B1] into the most active vitamin D3 known as 1,25-dihydroxyvitamin D [1,25(OH)$_2$D3], which may potentiate mineralization of bone *via* its role in the stimulation of calcium absorption in the intestine. Many immune cells also contain the machinery for the two-step conversion of vitamin D to 1,25(OH)$_2$D3[8]. Moreover, 1,25(OH)$_2$D3 can be produced locally in the pancreas from the main circulating form, 25(OH)D3, because 1 α-hydroxylase is present in islets[9]. 25(OH)D3 itself also has some biological activity, but the affinity of 1,25(OH)$_2$D3 is about 1000-fold higher than 25(OH)D3 for the vitamin D receptor (VDR). All metabolites of vitamin D are circulating in the bloodstream bound to the vitamin D-binding protein that has a different affinity for the individual metabolites[10]. Seasonal factors, geographical variations, differences in skin color, age, and changes in lifestyle may make certain subjects more susceptible to develop vitamin D insufficiency [defined as 25(OH)D3 concentrations 20-30 ng/mL or 50-75 nmol/L], or vitamin D deficiency [25(OH)D3 concentration < 20 ng/mL or < 50 nmol/L][11] (Table 1).

POSSIBLE MECHANISMS BY WHICH VITAMIN D MAY INFLUENCE GLUCOSE INTOLERANCE AND TYPE 2 DIABETES MELLITUS

The development of abnormal glucose tolerance and type 2 diabetes mellitus is always preceded by alterations in the function of pancreatic β-cells, insulin sensitivity, and systemic inflammation. Available data suggest that these mechanisms are influenced by vitamin D.

β-cell function of the pancreas

Responses of insulin to glucose load appears to be exclusively influenced by vitamin D. Vitamin D does not appear to affect basal insulin[12,13]. A positive role for vitamin D in the modification of the function of β-cells of the pancreas has been reported[14]. This role is mediated through several pathways, including direct stimulation of insulin secretion by vitamin D through the presence of vitamin D receptors (VDRs) in β-cells of the pancreas[14] and their expression of 1-α-hydroxylase enzyme[9]. Also, 1,25-(OH)$_2$D is able to activate transcription of the gene of human insulin and thus play an essential role in insulin secretion[15]. In mice, it has been shown that insulin secretory response may be impaired if the functional VDRs were absent[13]. Several animal studies have also shown that when those were supplemented with vitamin D, they became able to restore their insulin secretion[12,16-19]. In human studies, introduction of vitamin D was associated with improvement in release of insulin in some[20-23], not all[21,22,24], limited-scale short-term studies.

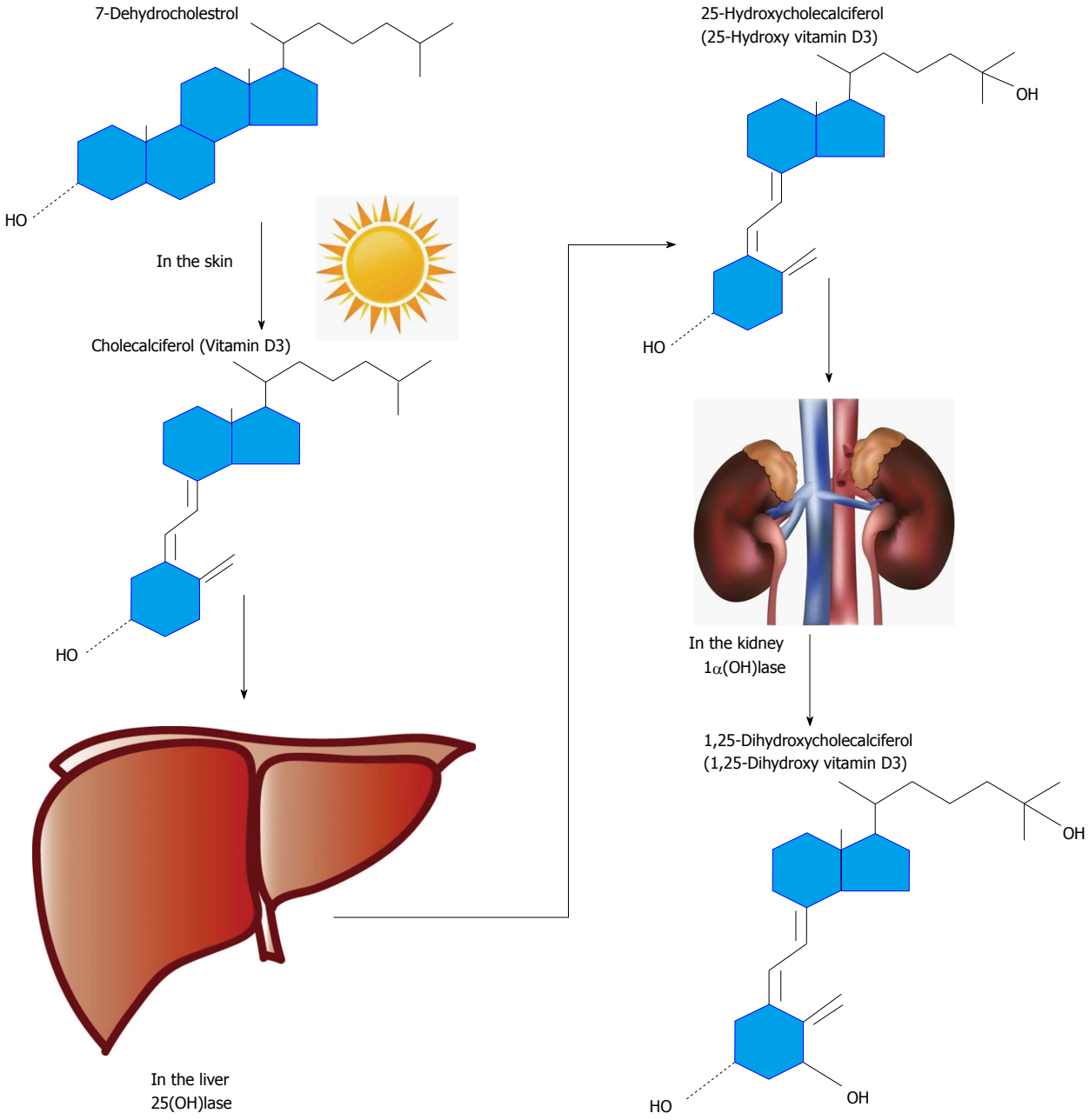

Figure 1 Schematic overview of the metabolism of vitamin D. Synthesis of vitamin D3 starts in the skin where 7-dehydrocholesterol is converted into vitamin D3 in response to UVB exposure. Vitamin D3 is hydroxylated by 25-hydroxylases in the liver. The resulting 25-hydroxyvitamin D3 is then hydroxylated in the kidney by 1α hydroxylase, to produce the final activated product, 1,25-dihydroxyvitamin D3.

Through its regulatory role of the calcium pool of β-cell intracellularly and extracellularly, vitamin D insufficiency appears to affect normal release of insulin[25] particularly in reaction to a glucose intake since the secretion of insulin is mediated by a calcium dependent mechanism. Some[20,21,26-28], compared with other[22,29], studies of variable cohorts including diverse baseline status of vitamin D have reported a link between deficiency of vitamin D and impairment of release of glucose-induced insulin. Moreover, a role of calbindin-D28k (a calcium-buffering protein in pancreatic beta cell) in calcium regulation and modulation of insulin release has been described[25].

Insulin insensitivity

Improvement in action of insulin may be mediated by vitamin D directly through the presence of VDRs in skeletal muscles[30], stimulation of expression of insulin receptors in bone marrow cells[31] and through vitamin D activation of peroxisome proliferator activator receptor-δ[32], a transcription factor involved in the control of metabolism of fatty acids in adipose tissue and skeletal muscle[33]. The indirect role of vitamin D is *via* the regulation of pools of intracellular and extracellular calcium and control of normal influx of calcium through the membranes of cells. Some[27,34] studies have demonstrated a negative association of vitamin D with

Table 1 Accepted cut-off values of 25 hydroxyvitamin D3 (25OHD3) that describe vitamin D status

Vitamin D status	25OHD3 (nmol/L)[1]
Sufficient (optimal)	> 75
Insufficient	50-75
Deficient	< 50

[1]Conversion factor, 1 nmol/L = 2.5 ng/mL.

insulin insensitivity, but this was not shown by others[22].

Inflammation

In the state of systemic inflammation that T2DM can create based on wide range of clinical studies[35-37], altered function of β-cells triggered by apoptosis of β-cell can develop due to the presence of elevated cytokines that can also induce insulin resistance directly. Vitamin D can act to lower systemic inflammation in general by interacting with components in the region of promotion of cytokine genes interfering with generation and action of cytokines through impeding the role of factors involved in nuclear transcription[38-40].

Specifically to insulin insensitivity, vitamin D was demonstrated to under-regulate the activation of nuclear factor-κB[38,40,41], which plays a regulatory role for genes of cytokines of pro-inflammation implied in resistance of insulin[42]. On the other hand, data from human research with inconsistent outcome that have directly assessed the association of vitamin D or calcium status and systemic inflammation in relation to type 2 diabetes mellitus were reported[43-46].

EVIDENCE FOR VITAMIN D LINK WITH INSULIN RESISTANCE

Several trials have demonstrated an association between deficiency of vitamin D with increasing body mass index. One of those was a population trial from Norway with data from 10229 subjects, revealing an inverse association of 25(OH)D concentrations with BMI which was not only seen in summer, but also in winter months[47]. So levels of 25(OH)D may change in seasons, but not body mass index. Furthermore, the same trial reported results from 2656 studied subjects in a longitudinal study between 1994 until 2008, which showed a negative predictor role for the changes of BMI in levels of 25(OH)D in that a reduction of more than 1 kg/m^2 in BMI, would result in an estimated increase of 2.8 ± 19.9 nmol/L in levels of 25(OH)D.

In a study of adults from North America by Devaraj *et al*[48], prediabetic state (state of a fasting plasma glucose concentration of 6.1-6.9 mmol/L, a 2 h glucose concentration of 7.8-11 mmol/L, or glycosylated hemoglobin of 5.7%-6.4%), a form of insulin resistance presentation, was noted to be associated with serum 25(OH)D in the first quartile in comparison with the fourth quartile in association with an adjusted odds ratio of 1.47[48]. The same study showed that in patients with metabolic syndrome, concentration of 25(OH)D was negatively associated with fasting glucose and homeostasis insulin resistance model of assessment.

Improvement in 25(OH)D status in T2DM patients was shown to be linked to some improvements in insulin sensitivity[27], but still, other parameters of insulin resistance like obesity did not change significantly with vitamin D supplementations in other studies. The data from the Norwegian study (The Tromsø study), also included an intervention arm where 93 subjects of varying BMI values received vitamin D at 40000 IU weekly for a year[47]. At the end of trial, increased vitamin D_3 doses were not associated with significant decrease in weight. The intervention showed that individuals with obesity needed bigger vitamin D doses than lean ones to achieve similar concentration of 25(OH)D, and a similar outcome to this was demonstrated in another study by Lee *et al*[49]. At the end of the trial with non-significantly different 25(OH)D values at baselines and vitamin D treatment doses, subjects with higher BMIs had lower concentrations of 25(OH)D compared with those of lower BMIs indicating that possibly body composition and insulin resistance in higher BMI subjects have a regulatory influence on vitamin D absorption, metabolism and/or storage.

The negative association between body weight, together with evidence of increased adiposity and low adiponectin levels, and low 25(OH)D concentrations also were shown in different age groups including both children and adolescents. Deficiency of vitamin D was prevalent in young Norwegian subjects[50], African-American adolescents[51], in both black and Caucasian youth[52] and tropical locations like Malaysia and Colombia[53,54].

Those prevalence studies remain with low scientific evidence since they are only observational and it is difficult to draw a causality relationship from them due to multiple confounders. Despite attempts to control those confounders, still full causality cannot be achieved.

DATA ON VITAMIN D LINK WITH T2DM

Large number of human trials, mainly cross-sectional and some longitudinal, have demonstrated a negative correlation of vitamin D status with predominant hyperglycemia. This correlation was shown both in children and adults, in each gender, and in diverse backgrounds of ethnicity[48,55-61]. Also have been reported that seasonal variation in diabetes control being worse during winter months when vitamin D levels in their lowest[62]. Beside prevalence, incidence of T2DM with decreased level of vitamin D has also been shown in majority of longitudinal but observational trials. It is therefore worth to go through the available observational or intervention trials.

Observational studies for T2DM incidence in association with altered vitamin D

In the recent review of systematic analysis of obser-

Table 2 Data of selected epidemiological studies on the relation between vitamin D level and markers of insulin resistance (A), insulin resistance (B) and type 2 diabetes (C)

Ref.	No. of subjects	Age, mean or range	Trial outcome
(A)			
Jorde *et al*[47]	10229	58	25OHD negatively associated with BMI
Lee *et al*[49]	95	68, 47-91	25OHD negatively related to BMI
Lagunova *et al*[50]	102	8-19	↑ prevalence of Vit D Def. (19%) and insuff. (> 50%) in obese
Suijder *et al*[60]	453	> 65	↑ BMI is associated with ↓ 25OHD
(B)			
Chiu *et al*[27]	125	26	+ve relation between 25OHD and insulin sensitivity
Nunlee-Bland *et al*[51]	34	10-20	↓ 25OHD is associated with insulin resistance
Shankar *et al*[61]	12719	> 20	↓ 25OHD is associated with pre-diabetes state
(C)			
Song *et al*[63]	76220	meta-analysis	inverse relation between 25OHD and risk for T2DM
Afzal *et al*[64]	9841	48-65	↓ 25OHD is associated with ↑ risk for T2DM
Pittas *et al*[65]	95243	meta-analysis	↓ incidence of T2DM in highest *vs* lowest 25OHD
Buijsse *et al*[69]	53088	50.9	HR of T2DM is ↓ with ↑ in 25OHD

T2DM:Type 2 diabetes mellitus; BMI: Body mass index.

vational studies, Song *et al*[63] described a reduction of 38% in relative risk in diabetes incidence for subjects with the highest compared with the lowest group of serum of 25(OH)D_3 level. 21 prospective studies, largely population-based studies with white subjects, were included in the analysis involving about 70000 participants. The relations of 25(OH)D concentration and risk of diabetes were weakened but remained significant following corrections for hypertension and BMI. The association was not influenced by gender, sample size of study, period of follow up time, diagnostic criteria for diabetes, or method of 25(OH)D assay. About 4% reduction in T2DM risk was seen for each increment of 10 nmol/L (4 ng/mL) in serum 25(OH)D_3 level. In similar review studies, but with smaller numbers, a meta-analysis found a higher relative risk of 50% for the development of T2DM in low *vs* high 25(OH)D concentrations[64]. In that last study, analyses stratified according to study design did not alter the appreciated association substantially.

Most of data analysis for risk of developing T2DM in relation to vitamin D status has used cutoffs categorizing vitamin D deficiency or insufficiency that is less clinically practiced in the last few years. In majority of trials, serum value of 25(OH)D above 50 nmol/L is considered sufficient while a large body of evidence supported by scientific agreement is considering a level above 75 nmol/L to be sufficient to execute its biological effect[11].

Even though serum level above 75 nmol/L of 25(OH)D could be beneficial to multiple physiological effects, its protective effect against developing T2DM compared to levels in the insufficient range (75-50 nmol/L) is doubtful or at least needs further investigation. In data from large number of participants of 9841 from The Copenhagen City Heart Study, a long-term prospective study with a median of 20 years follow up of the general population of Denmark, increased hazard ratios (HR) for T2DM with decreased concentrations of 25(OH)D by clinical severities and season quartiles were noted. For 25(OH)D less than 12.5 nmol/L compared with levels more than 50 nmol/L, the HR was 1.22, and was 1.35 for lowest compared with highest quartile[64]. This was not clinically significant when the values of more than 75 nmol/L is used as a sufficient level compared with values of 25(OH)D between 75-50 nmol/L (HR 0.91).

Serum vitamin D levels are influenced significantly by dietary habits, mainly consumption of dairy products. After a prospective follow up for 20 years, in a cohort of the Nurses Health Study, an inverse association between T2DM risk with total 25(OH)D and calcium intake was described[65]. The analysis showed that consumption of 3 or more *vs* only one daily dairy serving was associated with decreased risk of development of diabetes.

Several genetic studies have identified a relationship of circulating 25(OH)D with presence of polymorphisms of single nucleotide in six genetic regions[66-68]. In an observational study of Buijsse *et al*[69] where eight of those polymorphisms of single nucleotides, most strongly associated with 25(OH)D, were tested in relation to levels of 25(OH)D and T2DM incidence in an observational prospective case-control manner. In that study, it was found that in a population with relatively low serum values of 25(OH)D, 25(OH)D was inversely associated with T2DM risk, for concentrations of 25(OH)D below 45 nmol/L only (compared with higher levels), after controlling for measures of general and abdominal adiposity. After being adjusted for age, gender, center, and month of the year blood drawn, HR of T2DM per 5 nmol/L higher 25(OH)D was 0.92. But this study also found that genetically determined 25(OH)D was not related to T2DM across the entire 25(OH)D range or below 45 nmol/L. This latter finding argues against a strong causal relationship of 25(OH)D with T2DM but requires further investigation in larger research groups.

Caution has to be applied when making conclusions from observational studies due to possible multiple confounding factors affecting vitamin D status like age, race, dietary habits and level of activity, which are also known to play a role in increased risk for development of diabetes. Table 2 shows summary of selected epidemio-

logical studies on the association of vitamin D with markers of insulin insensitivity, pre-diabetic resistance to insulin and T2DM is displayed in Table 2.

Randomized intervention trials for the relation of vitamin D and T2DM

Direct evidence of a role for vitamin D in diabetes prevention and treatment is critically needed from interventional randomized studies before any conclusion can be made. Those needed intervention trials, ideally large-scale randomized trials, are lacking today. What is available are either data of scattered small-scale trials or some of post hoc data from analyses of somewhat larger studies on the influence of supplementation of vitamin D on parameters related to diabetes and those were either inconsistent or inconclusive, though vitamin D is known to have certain advantageous effects in subjects with increased diabetes risk[43,64,70,71]. There are several limitations that can make it difficult to draw conclusions of solid nature from the limited available-to-date small interventional trials. Some of those trials were intended mainly to assess outcomes on glycemia and the majority of them were underpowered. Also, there was a variation in the dosing of vitamin D for replacement, some of these studies used supraphysiological vitamin D doses at infrequent manner, while others used daily doses and this would potentially cause different pharmacokinetic effect on concentration of 25(OH)D and pharmacotherapeutic effects on target cells.

In description of some of those trials, data analysis of the well known randomized trial of Women's Health Initiative[72], in which about 50% of the women had 25(OH)D concentration less than 45 nmol/L, revealed no effect of administration of vitamin D3 at 400 IU and calcium at 1000 mg daily for 7 years on risk of diabetes (HR 1.01). Two smaller randomized trials tested the glycemic effect of applying vitamin D3 in subjects with impaired fasting glucose; the first one found that people using vitamin D3 daily at 700 IU and calcium at 500 mg for 3 years had a less rapid worsening of glycemia than those on placebo[43]. The second trial supplemented with vitamin D3 to get 25(OH)D levels between 150 and 225 nmol/L[73]. After 1 year, no effect was seen on incident diabetes. Together with the mixed findings of short-term trials on the influences of vitamin D on release of insulin and its sensitivity[73,74], the experimental evidence today is inconsistent.

CONCLUSION

In conclusion, data from non-interventional observational trials have shown a negative relationship between the status of vitamin D and parameters of insulin insensitivity and incidence of T2DM. A biological active position for vitamin D in both insulin secretion and action, and in the function of β-cells has been considered. However, definitive conclusion for a causative link for vitamin D with T2DM can not be drawn due to the missing of large-sized prospective observational investigations that use 25(OH)D as the target variable and the absence of randomized trials particularly designed to assess the influence of vitamin D on diabetes. Similar randomized prospective trials are needed to correctly explain the outcome of vitamin D administration as an interventional agent for preventing and managing diabetes. We anticipate that these future well designed randomized prospective trials to answer several important questions. Firstly, whether the daily interventional utilization of vitamin D in the pre-diabetic states works as a strong defensive tool against progression to type 2 diabetes? Secondly, whether the daily intake of vitamin D will be accompanied with significant glycemic improvement? And finally, whether supplementation of vitamin D to diabetics will delay or prevent some of the adverse diabetic complications or have positive effects on cardiometabolic outcomes in long term.

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MINIREVIEWS

Gestational diabetes: A clinical update

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Abstract

Gestational diabetes mellitus (GDM) is increasing in prevalence in tandem with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Much controversy surrounds the diagnosis and management of gestational diabetes, emphasizing the importance and relevance of clarity and consensus. If newly proposed criteria are adopted universally a significantly growing number of women will be diagnosed as having GDM, implying new therapeutic challenges to avoid foetal and maternal complications related to the hyperglycemia of gestational diabetes. This review provides an overview of clinical issues related to GDM, including the challenges of screening and diagnosis, the pathophysiology behind GDM, the treatment and prevention of GDM and the long and short term consequences of gestational diabetes for both mother and offspring.

Key words: Gestational diabetes; Diagnostic criteria; Treatment; Complications

Core tip: Gestational diabetes is increasing in prevalence coincidently with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Much controversy surrounds the diagnosis and management of gestational diabetes, making it an important subject to discuss as the risk of foetal and maternal complications are increased in gestational diabetes. This review provides an overview of issues related to gestational diabetes, including the challenges of screening and diagnosis, the pathophysiology behind gestational diabetes, the treatment and prevention of gestational diabetes and the long and short term consequences of gestational diabetes for both mother and offspring.

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INTRODUCTION

Gestational diabetes mellitus (GDM) occurs in about 5% of pregnancies but figures vary considerably depending upon the criteria used and demographic characteristics of the population. The prevalence is expected to increase as the epidemic of obesity continues[1]. Pregnancies affected by GDM impose a risk for both mother and child as the risk of cesarean and operative vaginal delivery, macrosomia, shoulder dystocia, neonatal hypoglycemia and hyperbilirubinemia is increased[2]. Women with a history of GDM are also at an increased risk of developing type 2 diabetes mellitus (T2DM) in the years following their pregnancy and their children have a higher risk of developing obesity and T2DM early in life[3].

For those reasons it is important to pay rigorous attention to GDM and the purpose of this review is therefore to cover a wide range of clinical issues related to GDM, including the challenges of epidemiology, diagnostic criteria and screening, the pathophysiology of GDM, the treatment and prevention of GDM and the long and short term consequences of GDM for both mother and child.

EPIDEMIOLOGY

It is problematic to determine the true prevalence of GDM. The prevalence varies worldwide and even within a country's population, depending on the racial and ethical composition of the residents. Accordingly, in the United States the prevalence is higher amongst African American, Hispanic American, Native American, Pacific Islander, and South or East Asian women than in Caucasian women[4]. Furthermore the prevalence of GDM differs depending on the variety of screening strategies (universal or selective), diagnostic criteria and the prevalence of T2DM in any specific country. While data from western countries are frequently reported, data from developing countries are sparse. Recently Jiwani *et al*[5] and Macaulay *et al*[6] tried to determine the prevalence of GDM worldwide, including developing countries. The prevalence was found to be ranging from < 5% in countries such as Pakistan, Belgium, Denmark, Estonia, Ireland, South Korea, South Africa and United Kingdom, to < 10% in Italy, Turkey, Brazil, United States, Morocco and Australia, to a prevalence as high as 20% in Bermuda and Nepal. A recent report from the International Diabetes Federation estimated that worldwide 16% of live births in 2013 were complicated by hyperglycemia during pregnancy[7] and it is most likely that the prevalence of GDM will increase due to the increase in risk factors like obesity and physical inactivity.

SCREENING AND DIAGNOSIS

Recently the American Diabetes Association (ADA) defined GDM as "diabetes diagnosed during pregnancy that is not clearly overt diabetes"[8]. Screening and diagnostic testing for GDM is however important in order to identify the women at risk for developing GDM and thereby reduce or prevent the risk of adverse events for both mother and child associated with GDM.

In most countries a selective screening is carried out, using parameters such as previous GDM, previous large for gestational age babies, diabetes (of any kind) in first degree relatives, pre-pregnancy adipositas, belonging to a particular ethnic group associated with a high prevalence of GDM, glucosuria, and high maternal age. By using selective screening there is a risk of missing GDM cases. On the other hand, selective screening could help to concentrate medical resources on subjects with the highest risk of complications.

Also, screening for preexisting diabetes in the very early weeks of pregnancy by the measurement of a fasting glucose is warranted. This is important because of the rising prevalence of T2DM at younger ages. Accordingly there is an increasing number of young women in their twenties and thirties presenting with undiagnosed preexisting T2DM.

Pregnant women have a higher physiological turnover of erythrocytes, rendering glycosylated hemoglobin (HbA1c) inadequate as a diagnostic tool, because of underestimation of the average glucose level. In fact a reduction of HbA1c is seen in normal pregnancy[9] Instead, a variety of oral glucose tolerance tests (OGTT) have been applied, but a consensus regarding screening for and classification of GDM is yet to be achieved globally[10]. However, a 2-h 75 g OGTT at 24-28 wk of gestation is now being recommended both by the European Association for the Study of Diabetes, International Association of Diabetes and Pregnancy Study Group (IADPSG), ADA and World Health Organization (WHO)[6].

The HAPO study recently demonstrated that no specific threshold for the risk of adverse events for both mother and child associated with GDM can be set as the risk increase is continuous[11]. Other studies[12-14] have supported the idea of lowering the diagnostic threshold in the diagnostic criteria for GDM, taking the maternal and foetal risks of hyperglycemia into consideration. In 2010 the IADPSG outlined new diagnostic criteria for GDM[15] based on the knowledge achieved in the HAPO study. This new guideline from IADPSG was adopted by the WHO in 2013[16] and ADA in 2014[8] and is based on the risk of adverse pregnancy outcomes As shown in Table 1 the threshold for a positive test is exceedance of one of the following three plasma glucoses; fasting plasma glucose ⩾ 5.1 mmol/L (⩾ 92 mg/dL), 1 h ⩾ 10.0 mmol/L (180 mg/dL), or 2 h ⩾ 8.5 mmol/L (153 mg/dL)[15]. In comparison the WHO recommended threshold in 1999 was fasting plasma glucose ⩾ 7.0 mmol/L (126 mg/dL) and in 1985 fasting plasma glucose ⩾ 7.8 mmol/L (140 mg/dL)[6].

It has been estimated that with this new diagnostic criteria the prevalence of GDM will increase to nearly 18%[11], which will have a major impact on the costs, the capacity of the health care systems, and the pathologization of pregnancies that were earlier categorized as normal. The vast majority of the women diagnosed with

Table 1 New (2013) World Health Organization recommendations for the diagnosis of gestational diabetes based on the general principles behind how the IADPSG criteria were derived

Gestational diabetes mellitus should be diagnosed at any time in pregnancy if one or more of the following criteria are met	
Fasting plasma glucose	5.1-6.9 mmol/L (92-125 mg/dL)
1-h plasma glucose following a 75 g oral glucose load	≥ 10.0 mmol/L (180 mg/dL)
2-h plasma glucose following a 75 g oral glucose load	8.5-11.0 mmol/L (153-199 mg/dL)

If fasting plasma glucose ≥ 7.0 mmol/L (126 mg/dL), and/or 2-h plasma glucose ≥ 11.1 mol/L (200 mg/dL) and/or random plasma glucose ≥ 11.1 mol/L (200 mg/dL) in the presence of diabetes symptoms overt diabetes is diagnosed.

GDM will however have mild hyperglycemia, requiring non-pharmaceutical treatment, including lifestyle modifications.

PATHOPHYSIOLOGY

In normal pregnancy, maternal tissues become progressively insensitive to insulin. This is believed to be caused partly by hormones from the placenta and partly by other obesity and pregnancy related factors that are not fully understood.

Skeletal muscle and adipose tissue are the main whole-body glucose disposable sites. In normal pregnancy, insulin-mediated whole-body glucose disposal decreases by 50% and in order to maintain a euglycemic state, the woman must increase her insulin secretion by 200%-250%[17].

GDM develops when the pregnant woman is not able to produce an adequate insulin response to compensate for this normal insulin resistance.

GDM is observed in obese as well as in lean women. However, the pathophysiology behind the disease is believed to differ between these groups. In obese women, the pathophysiology is primarily characterized by the pregnancy-induced insulin resistance being amplified by the already elevated pre-pregnant insulin resistance level. The elevated insulin resistance level is a known factor in the metabolic syndrome. In lean women, the same factors seem to play a role but a defect in the first-phase insulin response contributes to a larger extend[18].

These defects culminate in a disruption of the action of insulin in maintaining glucose levels, resulting in maternal hyperglycaemia. Glucose is transferred *via* the placenta to the fetus. Maternal hyperglycaemia therefore stimulates a foetal hyperinsulinaemia to counter the excess placental glucose transfer. The high insulin level in the fetus stimulates growth which results in foetal macrosomia (birth weight over 4000 g)[19].

RISK FACTORS FOR DEVELOPING GDM

There is a range of established risk factors for GDM, chief amongst which are the following. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported that a higher pre-pregnant BMI and the BMI at 28 wk are strongly correlated to increased insulin resistance at 28 wk[11]. Adipose tissue is, like the placenta, believed to produce a large amount of diabetogenic adipokines. Especially the adipokine TNF-α, which the placenta likewise produces, is suspected to play an important role in insulin resistance pathways. This could be one explanation to the elevated pre-pregnant insulin resistance level seen in obese women[20].

As mentioned previously, ethnicity seems to play an important role as well. Berkowitz *et al*[21] reported that the United States Native Americans, Asians, Hispanics, and African-American women have a higher risk of GDM compared to non-Hispanic white women. In addition studies have shown that women from Asia are at very high risk of developing GDM and the increased insulin resistance is observed at much lower BMI levels when compared to European women. Retnakaran *et al*[22]. reported that Asian women's pre-pregnancy BMI has a greater influence on the pregnancy related insulin resistance than that of Caucasian women.

Cypryk *et al*[23] reported that maternal age over 25 years and previous GDM are strongly correlated to development of GDM. These findings are in agreement with other authors[23-25]. In addition Polycystic Ovary Syndrome, multiparity, twin pregnancy and a family history of diabetes are well known risk factors[26].

COMPLICATIONS DURING PREGNANCY AND BIRTH

Women with GDM are at higher risk of hypertensive disorders including gestational hypertension, preeclampsia, and eclampsia. In the HAPO study, 5.9% had gestational hypertension and 4.8% had preeclampsia. The study showed that the glucose level at the first glucose tolerance test was positively correlated with the risk of preeclampsia[27]. Likewise, Rowan *et al*[28] reported that 5% had gestational hypertension and 6.3% had preeclampsia.

The HAPO study, found a direct correlation between Cesarean section rate and maternal glycemia with an overall frequency of 23.7%[27]. Gorgal *et al*[28] reported a non-elective cesarean section rate for women with GDM of 19.5% compared to 13.5% for non-diabetic women.

Macrosomia in newborns of diabetic mothers is characterized by increased body fat[16]. The IADPSG study found that percentage of body fat in newborns, maternal glycemia and foetal insulin levels estimated by cord C-peptide level were strongly positively correlated[15]. Thus maternal glycemia is directly related to neonatal adiposity. Although rare, shoulder dystocia is a serious complication of childbirth. A clear association between increased foetal size and the risk of shoulder dystocia has been shown once the birth weight exceeds 4 kg[29].

In older studies, the risk of stillbirth was increased fourfold[30]. In more recent studies, this risk is found to

be lower; probably due to the initiation of monitoring and treatment of GDM. In the HAPO study, there was no increased risk of prenatal death with increased maternal glucose levels[11]. In comparison, Crowther *et al*[31] observed five deaths in the Routine Care Group and none in the Treatment Group.

MATERNAL LONG-TERM CONSEQUENCES OF GDM

GDM is not only associated with adverse pregnancy outcomes, such as macrosomia, increased caesarian section rates, hypertensive disorders and foetal hyperinsulinaemia[32,33], but also significantly increases the risk for long-term problems for both mothers and their offspring.

T2DM

Women who have had GDM have a substantially increased risk for development of T2DM, even though most women return to a euglycaemic state shortly after delivery[34-36]. The evidence of this association is massive, but the magnitude of the risk varies among studies, primarily explained by differences in length of follow-up, number of women participating in follow-up, diagnostic criteria and in the selection of the population[37]. A Danish study found that 40% of women with diet-treated GDM had developed diabetes 10 years after the index pregnancy. Compared to the 30-60-year-old females in the background population, the incidence of diabetes was increased 10 fold[36]. A systematic review of 20 studies found an at least 7 fold increase in the risk of developing T2DM, when comparing women with a pregnancy complicated by GDM to women with a normoglycaemic pregnancy[34]. In conclusion, GDM is one of the most predictive factors for the development of T2DM later in life. These women should be followed up with an OGTT 2-3 mo after delivery and then a yearly follow-up, ideally with an OGTT. Furthermore, a yearly fasting glucose test will allow detection of the development of T2DM early in these women.

The specific biological link between GDM and T2DM remains unclear. Both disorders are characterized by insulin resistance and/or abnormal insulin secretion. In addition studies provide evidence that several of the known T2DM risk genes are more frequent in women with previous GDM[38], and many of the risk factors are the same, such as a raised body-mass index, high age, family history of diabetes and Asian and black ethnicity[37,39]. It thus appears plausible that the pathogenesis is overlapping, and GDM may serve to identify women at high risk of future T2DM[34,36].

Metabolic syndrome and cardiovascular disease

GDM may also increase a woman's risk of the metabolic syndrome and cardiovascular disease (CVD) postpartum. The metabolic syndrome is characterized by several risk factors, including central obesity, hypertension, insulin resistance and dyslipidemia. These risk factors are also associated with the development of CVD and T2DM, and the metabolic syndrome has been demonstrated to increase the risk of both outcomes[40]. The abnormalities of the metabolic syndrome and a high risk health profile are more frequent among women with previous GDM. The prevalence of the metabolic syndrome is found to be 3 times as frequent in Danish women with previous diet-treated GDM compared to population-based and age-matched control women[41]. Another study has demonstrated that the 3 mo postpartum prevalence of the metabolic syndrome increases progressively from 10% in women with normoglycaemic pregnancies to 17.6% in women with gestational impaired glucose tolerance and to 20% in women with previous GDM[42]. These results suggest that dysglycemia in pregnancy may provide an opportunity to detect otherwise unrecognized risk conditions, such as the metabolic syndrome and consequently allow targeted intervention to prevent diabetes and CVD.

The risk of CVD is found to be approximately 70% higher in women with previous GDM compared with women having normoglycaemic pregnancies when followed for 11.5 years after the index pregnancy[43]. The increased risk may also extend to women with only mild glucose intolerance during pregnancy[44]. When adjusting for the incidence of T2DM, the association was attenuated in both studies.

The increased risk of CVD in women with prior GDM is attributable to several interacting factors, primarily including the development of overt T2DM and the increased risk of the metabolic syndrome and vascular dysfunction[44]. Therapeutic interventions to prevent the development of T2DM may therefore reduce the risk of CVD, and a potential modification of cardiovascular risk factors may also help to prevent development of CVD in women with a history of GDM.

LONG TERM EFFECTS IN OFFSPRING OF WOMEN WITH GDM

Offspring of women with a history of GDM are also at increased long-term risk of developing metabolic diseases such as obesity, T2DM and the metabolic syndrome. This long-term risk depends on genetic susceptibility and is further modulated by the postnatal environment. In recent years focus has been on the phenomenon of epigenetic transmission of acquired characteristics from mother to child due to perinatal programming of the fetus[45]. Maternal glucose easily crosses the placenta and as a consequence maternal hyperglycemia leads to intrauterine hyperglycemia, which induces foetal hyperinsulinemia and possible modification of growth and future metabolism of the fetus (fuel-mediated teratogenesis)[46,47]. Also worth noticing, is the finding that the relation between birth weight and risk of T2DM is U-shaped and therefore both infants with decreased and those with increased birth weight are at increased

risk of developing T2DM as compared to persons being born with a normal birth weight[48].

Animal studies have convincingly shown that intrauterine exposure to maternal diabetes is associated with an increased risk of abnormal glucose tolerance, diabetes and obesity in offspring[49]. Although it is difficult to study the effect of intrauterine hyperglycemia separately from a genetic effect in humans observational studies among the Pima Indians have added evidence for an epigenetic mode of diabetes transmission. Thus children of diabetic mothers had a 6 fold increased risk of developing T2DM compared to children born to non-diabetic mothers[50]. Another study conducted in the Pima Indian population strengthened this association by showing a higher incidence of diabetes in siblings born after a maternal diagnosis of diabetes compared to a sibling born before the maternal diagnosis of diabetes (OR: 3.0, $P < 0.01$), which partly eliminates the genetic disposition. A greater frequency of diabetes is also seen in offspring of mothers with T2DM than offspring of T2DM fathers[51]. These results are not directly applicable to other populations, as Pima Indians have a remarkably high incidence of T2DM, but they clarify the importance of intrauterine exposure to hyperglycemia, even within a population with a strong genetic inheritance of T2DM[51].

A Danish long-term follow-up study based primarily on a Caucasian population found a high prevalence of T2DM and pre-diabetes in adult offspring of mothers with diet-treated GDM and in offspring of mothers with type 1 diabetes compared with the background population [Adjusted OR: 7.76 (95%CI: 2.58-23.39) *vs* 4.02 (95%CI: 1.31-12.33)]. These findings support the hypothesis that a hyperglycemic intrauterine environment plays a role in the pathogenesis of T2DM[52] and are in accordance with earlier studies on children with a mixed ethnic composition, finding a similar prevalence of impaired glucose tolerance in offspring born to mothers with GDM[53,54]. T2DM is characterized by both reduced insulin sensitivity and impaired B-cell function, but little is known about how these precursors are changed in the offspring after an exposure to maternal hyperglycemia in pregnancy. A recent study found that offspring exposed to intrauterine hyperglycemia due to GDM, primarily have reduced insulin sensitivity, but also a significantly lower relative insulin release taking insulin sensitivity into account (disposition index) when compared with the background population. The absolute insulin release did not differ significantly between the groups[55].

Two other possible long-term consequences of pregnancies complicated by GDM is the development of the metabolic syndrome and obesity in the offspring. Development of obesity in offspring exposed to maternal diabetes in utero is found in the Pima Indian population, where the mean BMI was 2.6 kg/m^2 higher in offspring born to diabetic mothers compared to offspring born to non-diabetic mothers[51]. This association is also seen in the multi-ethnic EPOCH study, where children of mothers with primarily GDM had a higher increase in BMI growth velocity than unexposed controls, with the increase starting at the age of 10 to 13[56]. According to a recent study, offspring of Caucasian women with GDM had a 2-fold increased risk of developing obesity and a 4-fold increased risk of the metabolic syndrome compared to the background population. This study also concludes that genetics play a major role in the development of the metabolic syndrome and obesity together with an effect of intrauterine hyperglycemia[57]. The prevalence of obesity increases worldwide among all age groups and some of the predisposition to obesity in children may be due to epigenetic foetal programming. Randomized trials are needed to clarify the possible causal relationship between maternal hyperglycemia in pregnancy and the mentioned cardiovascular risk factors in human offspring.

TREATMENT OF GDM

Recently two large randomized controlled trials have been carried out to prove that identification and treatment of GDM and even mild carbohydrate intolerance during pregnancy confer a benefit. Thus the Australian Carbohydrate Intolerance Study in Pregnant Women, a large, randomized trial of treatment for gestational diabetes mellitus, concluded that treatment reduces serious perinatal complications and may also improve health-related quality of life using treatment of gestational diabetes in the form of dietary advice, blood glucose monitoring, and insulin therapy as required for glycemic control[31]. The American Maternal-Fetal Medicine Units Network study provided further compelling evidence that among women who have GDM and normal fasting glucose levels, treatment that includes dietary intervention and insulin therapy, as necessary, reduces rates of foetal overgrowth, cesarean delivery, and preeclampsia[58].

Accordingly, the primary intervention recommended to women diagnosed with GDM is dietary counseling in combination with physical activity and self-monitoring of blood glucose[59,60]. If these measures are insufficient in terms of achieving optimal glycemic control subcutaneous insulin therapy is the therapy of choice as insulin does not cross the placenta and is therefore considered harmless to the foetus. However insulin is relatively expensive and difficult to administer. It requires education to ensure a safe administration and it is associated with an increased risk of hypoglycemia and weight gain. The use of safe and effective oral agents may therefore offer advantages over insulin but has not yet been formally approved for GDM therapy in all countries[61]. A large randomized controlled trial was performed by Rowan *et al*[62] in which 751 women with GDM at 20 to 33 wk of gestation were assigned to open treatment with metformin or insulin if lifestyle intervention had failed to achieve glycemic control. Three hundred and sixty-three women were assigned to metformin. 92.6% continued to receive Metformin until delivery and 46.3% in the Metformin group received supplemental insulin. The authors concluded that metformin, alone or with supplemental insulin, was not associated with increased

perinatal complications as compared with insulin. Thus the treatment with Metformin was considered safe and effective and moreover, the women preferred metformin to insulin treatment. Further follow-up data are however necessary to establish long-term safety.

Another randomized controlled trial included 404 women between 11 and 33 wk of gestation with singleton pregnancies and GDM that required treatment and assigned them to either glyburide or insulin. All the women received dietary advice and eight women in the glyburide group required additional insulin therapy. There were no significant differences between the glyburide and insulin groups regarding macrosomia, neonatal hypoglycemia, lung complications or foetal abnormalities and it was concluded that glyburide is a clinically effective alternative to insulin therapy[63].

Other studies show that both metformin and sulfonylurea have been increasingly and safely used in the treatment of GDM[64]. However, both glyburide and metformin cross the placenta and given the growing evidence of epigenetic foetal programming in utero, administration of drugs potentially affecting foetal metabolism is of major concern and as long term follow-up data on both mother and offspring are lacking oral antihyperglycemic agents should be used with caution.

Vitamin D and GDM

A growing body of epidemiological evidence suggests a possible association between vitamin D deficiency/insufficiency and GDM, maternal obesity and adverse maternal, neonatal and infant outcome[65]. The molecular and cellular mechanisms with respect to the interaction between vitamin D and GDM are only partly understood. However, it appears that vitamin D acts directly on pancreatic beta cells through expression of the vitamin D receptors as well as through the enzyme 25(OH)D-1-alfa-hydroxylase by regulating intracellular calcium to increase insulin secretion and by attenuating systemic inflammation associated with insulin resistance[66,67]. The association between vitamin D and glucose metabolism in GDM has been investigated in several observational studies[65] but large randomized controlled trials are lacking and it remains to be determined whether vitamin D supplementation can reduce the risk of developing GDM and/or improve glycemic control in diabetic pregnant women with vitamin D deficiency/insufficiency.

As stated above lifestyle counseling concerning diet and exercise is one of the cornerstones in the treatment of GDM, but recently it was also reported that a healthful diet was associated with a lower risk of T2DM among women with a history of GDM[68]. Additionally, newly published results from a large prospective study indicate that increasing physical activity may help lower the risk of progression from GDM to T2DM[69].

CONCLUSION

Worldwide there has been a dramatic increase in the prevalence of overweight and obesity in women of childbearing age. Overweight and obese women have an increased risk of developing GDM leading to complications during pregnancy, birth and neonatally. The clinical management of obese pregnant women and women with GDM is a challenge and puts additional stress on the healthcare system. In addition it seems more and more clear that maternal metabolic characteristics are crucial determinants of insulin resistance during pregnancy and in offspring and interventions, especially in the form of exercise, weight loss and a healthy diet before, during and after pregnancy might be a key to prevent the vicious circle that contributes to the epidemic of obesity, insulin resistance and T2DM.

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MINIREVIEWS

Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review

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Abstract

Steroids are drugs that have been used extensively in a variety of conditions. Although widely prescribed for their anti-inflammatory and immunosuppressive properties, glucocorticoids have several side effects, being hyperglycemia one of the most common and representative. In the present review, we discuss the main epidemiologic characteristics associated with steroid use, with emphasis on the identification of high risk populations. Additionally we present the pathophysiology of corticosteroid induced hyperglycemia as well as the pharmacokinetics and pharmacodynamics associated with steroid use. We propose a treatment strategy based on previous reports and the understanding of the mechanism of action of both, the different types of glucocorticoids and the treatment options, in both the ambulatory and the hospital setting. Finally, we present some of the recent scientific advances as well as some options for future use of glucocorticoids.

Key words: Steroid; Hyperglycemia; Diabetes mellitus; Treatment; Insulin

Core tip: Steroids are drugs that have been used extensively in a variety of conditions. Although widely prescribed for their anti-inflammatory and immunosuppressive properties, glucocorticoids have several side effects, being hyperglycemia one of the most common and

representative. We present the pathophysiology of corticosteroid induced hyperglycemia as well as the pharmacokinetics and pharmacodynamics associated with steroid use.

Tamez-Pérez HE, Quintanilla-Flores DL, Rodríguez-Gutiérrez R, González-González JG, Tamez-Peña AL. Steroid hyperglycemia: Prevalence, early detection and therapeutic recommendations: A narrative review. *World J Diabetes* 2015; 6(8): 1073-1081 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i8/1073.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i8.1073

INTRODUCTION

Steroids are drugs that have been used extensively in a variety of conditions, both acute and chronic[1]. At supraphysiological doses, they reduce the synthesis of pro-inflammatory cytokines, T-cell function, and antibody Fc receptor expression, which activate anti-inflammatory and immunosuppressive processes, making them the cornerstone in treatment of numerous inflammatory diseases[2,3].

Despite their efficacy, their use is limited by the wide variety of side effects, which can be divided into three categories: immediate, gradual and idiosyncratic. Immediate effects include fluid retention, blurred vision, mood changes, insomnia, weight gain, and modulation of the immune response. The more gradual effects are those related to endocrine metabolism, especially hyperglycemia, osteopenia with subsequent osteoporosis, dyslipidemia, central obesity, and adrenal suppression. Additionally, acne, skin thinning, and dyspepsia are considered of gradual onset. Some of the idiosyncratic effects are avascular necrosis, cataracts, open-angle glaucoma and psychosis[3-5].

Steroids are the main cause of drug-induced hyperglycemia[4]. They not only exacerbate hyperglycemia in patients with known diabetes mellitus (DM), but also cause DM in patients without documented hyperglycemia before the initiation of glucocorticoids (GC) therapy[1,6], with an incidence that can reach up to 46% of patients, and increases in glucose levels up to 68% compared to baseline[7-9]. Furthermore, in some populations they can precipitate acute complications such as nonketotic hyperosmolar state, and diabetic ketoacidosis[10] and in a few instances death, especially in patients with pre-existing DM.

EPIDEMIOLOGY AND RISK FACTORS

Exacerbated and uncontrolled hyperglycemia is a common complication in patients with DM and carbohydrate intolerance as previously documented[11] Moreover, DM incidence in patients without a prior history of hyperglycemia to steroid use varies from 34.3% to 56%[12,13], with a relative risk ranging from 1.36 to 2.31, and a number needed to harm ranging from 16-41 for 1-3 years of use, according to several authors[14-16]. In terms of the steroid presentation, only oral GCs have demonstrated to increase the risk of diabetes in up to 2% of incident cases in a primary care population; there is either minimal or no association of incident diabetes with prescribing of GC-containing in-halers, topical preparations, eye drops, or infrequent GC injections[17].

The main risk factors that have been identified as predictors of developing diabetes are: the dose and type of steroid, odds ratio (OR) (OR: 1.01, 95%CI: 0.996-1.018)[18,19], duration of treatment[9], a continuous GC scheme (OR: 2.0, 95%CI: 1.29-3.1)[12], older age (OR: 1.05, 95%CI: 1.02-1.09)[20], HbA1c, and body mass index (OR: 2.15, 95%CI: 1.12-4.13)[11,14,21]. In addition, there are population groups with a greater risk of developing hyperglycemia during treatment with steroids, among these are patients with a history of gestational DM, a family history of diabetes (OR: 10.29, 95%CI: 2.33-45.54), concomitant use of mycophenolate mofetil (OR: 4.80, 95%CI: 1.32-17.45) and calcineurin inhibitors, abnormal fasting glucose, and impaired glucose tolerance[3,8,19,22].

In the hospital setting, there is evidence that more than half of the patients receiving high-dose steroids develop hyperglycemia, with an incidence of 86% of at least one episode of hyperglycemia and 48% of patients presenting a mean blood glucose $\geqslant$ 140 mg/dL[23]. The main associated factors related to inpatient hyperglycemia are previous history of DM, a higher prevalence of comorbidities, prolonged treatment with steroids and older age[9,23].

PATHOPHYSIOLOGY

GC's provide a substrate for oxidative stress metabolism increasing lipolysis, proteolysis, and hepatic glucose production[4]. The mechanism responsible for glucose intolerance after GC administration is similar to that of type 2 DM since steroids increase insulin resistance, which can be up to 60%-80% depending on the dose and type used[14,15].

Among the notable factors that modify the biological effects of steroids, there is the enzymatic activity of 11β-hydroxysteroid dehydrogenase, which is classified into two types: type 1, expressed in liver and adipose tissue and amplifies the local action of steroids to convert cortisone to cortisol, and type 2, which predominates in renal tissue and reduces the effect of converting cortisol to cortisone[4].

Skeletal muscle is responsible for 80% of postprandial glucose storage and represents the largest reserve of glycogen in the body. Its storage is totally dependent on the presence of insulin and the availability of the glucose transporter type 4 (GLUT4) glucose transporter in the cell membrane. Steroids induce insulin resistance by directly interfering with signaling cascades, mainly the GLUT4 transporter, within muscle cells, with the subsequent 30%-50% reduction in insulin-stimulated glucose uptake and a 70% reduction in insulin-stimulated

Table 1 Pathophysiology of corticosteroid-induced hyperglycemia

Increase in insulin resistance with increased glucose production and inhibition of the production and secretion of insulin by pancreatic β-cells
Corticosteroids increase endogenous glucose production, increment in gluconeogenesis and antagonizing the metabolic actions of insulin
Enhance the effects of other counterregulatory hormones, such as glucagon and epinephrine, which increase the endogenous synthesis of glucose
Also been shown that the expression of the nuclear receptor peroxisome proliferator-activated receptor α is necessary for the increment in endogenous glucose production induced by corticosteroids
Corticosteroids reduce peripheral glucose uptake at the level of the muscle and adipose tissue
Costicosteroids also inhibit the production and secretion of insulin from pancreatic β-cells and induce β-cell failure indirectly by lipotoxicity

glycogen synthesis[24,25]. On the other hand, steroids are responsible for the catabolism of proteins with the subsequent increase in serum amino acids, which also interfere with insulin signaling in the muscle cell. Finally, they increase lipolysis, resulting in an increase in serum free fatty acids and triglycerides. These promote the accumulation of intramyocellular lipids (acetyl coenzyme A, diacylglycerol and ceramide), reducing the entry and storage of intramuscular glucose[4].

In the fasting state, the liver maintains euglycemia *via* gluconeogenesis and glycogenolysis, effects that are counteracted by insulin after food intake. GCs antagonize the metabolic effects of insulin, particularly in the postprandial state through the induction of enzymes that promote gluconeogenesis, increased lipolysis and proteolysis, increased mitochondrial activity, the enhancement of the effects of counterregulatory hormones, such as glucagon and epinephrine, and the induction of insulin resistance *via* the nuclear peroxisome proliferator-activated receptor (PPAR) α[4,21,25].

At the level of adipose tissue they promote the deposition of fat in viscera, while reducing peripheral reserves. Steroids have direct effects on various adipokines: (1) promoting the expression of resistin and adipokinines, which influence glucose tolerance; (2) decreasing the expression of adiponectins, which promote insulin sensitivity; and (3) stimulating expression and secretion of leptin. Finally, they are responsible for increasing triglyceride hydrolysis in adipocytes[4]. These effects have the final result of increased plasma levels of non-sterified fatty acids, which accumulate within muscle cells and reduce glucose uptake by interfering with insulin signaling[24,25].

It has been shown that GC's alter the function of pancreatic beta cells through the reduction of GLUT2 and glucokinase receptor expression at the same time increasing the activity of glucose-6-phosphate dehydrogenase, with the consequent alteration in β-oxidation. Additionally, they reduce insulin synthesis and it is thought that they reduce cell mass through the induction of beta cell apoptosis. Likewise, in response to the decrease in insulin sensitivity, the pancreatic beta cell normally increases insulin secretion to maintain glucose homeostasis, but at times this increase is not sufficient to compensate for the insulin resistance resulting in hyperglycemia[4,15].

Based on the aforementioned, GC's increase insulin resistance with the subsequent state of hyperinsulinism. In healthy subjects, this mechanism is compensated by an increase in pancreatic insulin secretion, causing serum glucose levels to remain within normal range[14]. However, in susceptible populations, such as normoglycemic individuals with reduced insulin sensitivity and a low rate of production of the same prior to steroid use, this offsetting effect is lost, resulting in hyperglycemia[4] (Table 1).

PHARMACOKINETICS AND PHARMACODYNAMICS

Steroids of adrenal origin are synthesized from cholesterol, and their secretion follows a circadian pattern and a pulsatile ultradian rhythm. Normal secretion ranges from 8 to 15 mg/d, of which 10% circulates in free form, the rest is bound to carrier proteins, mainly albumin and cortisol binding globulin. The plasma half-life ranges from 80-270 min depending on the type of GC's used, with an action in tissues that lasts for 8-12 h. They are metabolized in the liver and their conjugated metabolites are excreted mainly by the kidneys[5,25,26].

The development of insulin resistance is mainly postprandial and varies depending on the type of steroid used: intermediate-acting and long-acting GCs. Prednisone and methylprednisolone are classified as intermediate-acting GCs, with a peak of action 4-6 h following administration. Their effect on glucose levels is mainly during the afternoon and night without effect in fasting glucose when they are administered in a single dose. On the other hand, they cause persistent hyperglycemia when administered in divided doses. Dexametasone fits in the long-acting GCs, with a steroid hyperglycemia that lasts for more than 24 h, with a slight decline during an overnight fast[5,25,26].

The effect of steroids is usually transient and reversible. As steroid doses are reduced, their effect on endocrine metabolism returns to baseline and drug-induced diabetes is expected to resolve; however, this is not true in all cases[1,6]. There are few studies that describe the effect of long-term use of GCs on pancreatic function and the development of DM. According to recently published data, GC's are likely to cause the greatest impact when it is administered acutely, especially during the second and fourth week, with a spontaneous remission in the majority of patients when a phenomenon of adaptation reduces the extent to which

glucose levels increase[12,27].

EFFECTS OF STEROID HYPERGLYCEMIA

Despite its frequency, little is known about the impact of hyperglycemia associated with steroid use on clinical comorbidities and mortality. It is known that rheumatic diseases *per se* represent an important cardiovascular risk factor, which makes them the leading cause of premature mortality in these patients. Therefore, it is thought that the coexistence of inflammatory diseases and steroid-induced hyperglycemia may lead to worse cardiovascular consequences[3,10]. Similarly the diabetic patient possesses a traditional cardiovascular risk factor for microvascular and macrovascular complications.

Fluctuations in serum glucose levels have been associated with increased cardiovascular mortality associated with increased LDL cholesterol, endothelial dysfunction, activation of the coagulation cascade, increased pro-inflammatory cytokine production, and oxidative stress resulting in macrovascular disease progression[2]. Several studies have reported that transient increases in serum glucose are associated with acute inflammatory processes and endothelial dysfunction in both diabetic and non-diabetic patients[14].

In the hospitalized patient, acute hyperglycemia is associated with increased hospital stay, repeated emergency room visits, risk of admission to intensive care, higher risk of infection rates, poor wound healing and higher hospital mortality rates[9,23,28]. In susceptible populations such as the elderly, persistent hyperglycemia associated with GC use can precipitate hyperglycemic hyperosmolar states, which would require frequent hospital admissions for aggressive hydration and insulin therapy, as well as increased complications related to inpatient hyperglycemia[19]. Additionally, steroid hyperglycemia represents a strong predictor of graft failure in the transplant population with a 2-3 fold increased risk of fatal and non-fatal cardiovascular events as compared with non-diabetic patients[29,30].

DIAGNOSIS

All patients who are started on steroid treatment should have a baseline glucose, as well as education on daily self-monitoring of glucose[6,8]. Daily monitoring should be started when hyperglycemia above 180 mg/dL is identified in more than one occasion in the presence or absence of symptoms associated with hyperglycemia[1]. The diagnosis of steroid hyperglycemia is similar to the current criteria established by the American Association of Diabetes: blood glucose level of $\geqslant$ 126 mg/dL, glycemia at any time $\geqslant$ 200 mg/dL, HbA1c > 6.5% or blood glucose > 200 mg/dL 2 h after an oral glucose load[31].

Based on the pathophysiology and pattern of GC-induced hyperglycemia it seems that some of the current criteria for diagnosis of DM underestimate the diagnosis itself. Since steroid-induced diabetes is detected mainly in the postprandial state, we do not recommend the use of fasting glucose as well as the glucose tolerance curve as reliable diagnostic methods, because there is a high possibility of losing some of the hyperglycemic patients. According to observations in previous studies, postprandial glucose determinations and/or HbA1c determinations are suggested as a screening examination with long-term steroid use[21,32,33]. The postprandial glycemia after lunch offers the greatest diagnostic sensitivity, especially when intermediate-acting GCs are administered in a single morning dose.

In hospitalized patients, monitoring should start with capillary glucose determination from the start of steroid treatment. Since almost 94% of cases of hyperglycemia develop within 1-2 d of initiation of steroid therapy in the hospital setting, in nondiabetic patients who maintain glucose levels < 140 mg/dL without insulin requirements for 24-48 h, glycemic monitoring can be discontinued[23]. On the other hand, in patients with glucose levels > 140 mg/dL with persistent insulin requirements, a basal/bolus subcutaneous insulin scheme must be established. Additionally, in patients with severe and/or persistent hyperglycemia despite the subcutaneous scheme, insulin by infusion pump should be started[9,33,34].

Several protocols to detect patients at risk of steroid-induced hyperglycemia are being studied. This is based on the hypothesis that abnormalities in insulin secretion and loss of beta cell function present in pre-diabetic individuals can be exacerbated in response to an increase in insulin requirements secondary to GC exposure. Abdelmannan *et al*[18] recently reported the use of a "stress test", in which the administration of 8 mg dexamethasone provides timely detection of increases in serum glucose, C-peptide, and insulin in at risk population, whereby one can predict this complication prior to the usual dose of the steroid**.** However, it is necessary to develop further studies to confirm its usefulness.

TREATMENT OF STEROID HYPERGLYCEMIA

Due to differences in steroid dose and the scheme used, the approach to hyperglycemia should always be individualized[35]. A complete evaluation of the degree of pre-existing glucose intolerance, the patient's clinical condition, the degree of hyperglycemia, the type, dose and frequency of administration of the corticosteroid compound and the mechanism of action, pharmacokinetics and pharmcodynamics of the different hypoglycemic drugs must be made in order to determine the best treatment approach in each patient[25]. When selecting the best treatment the first consideration to make is whether to use oral hypoglycemic drugs or insulin (Figure 1).

ORAL HYPOGLYCEMIC DRUGS

There is little information on the therapeutic efficacy of oral agents in steroid-induced hyperglycemia. In patients

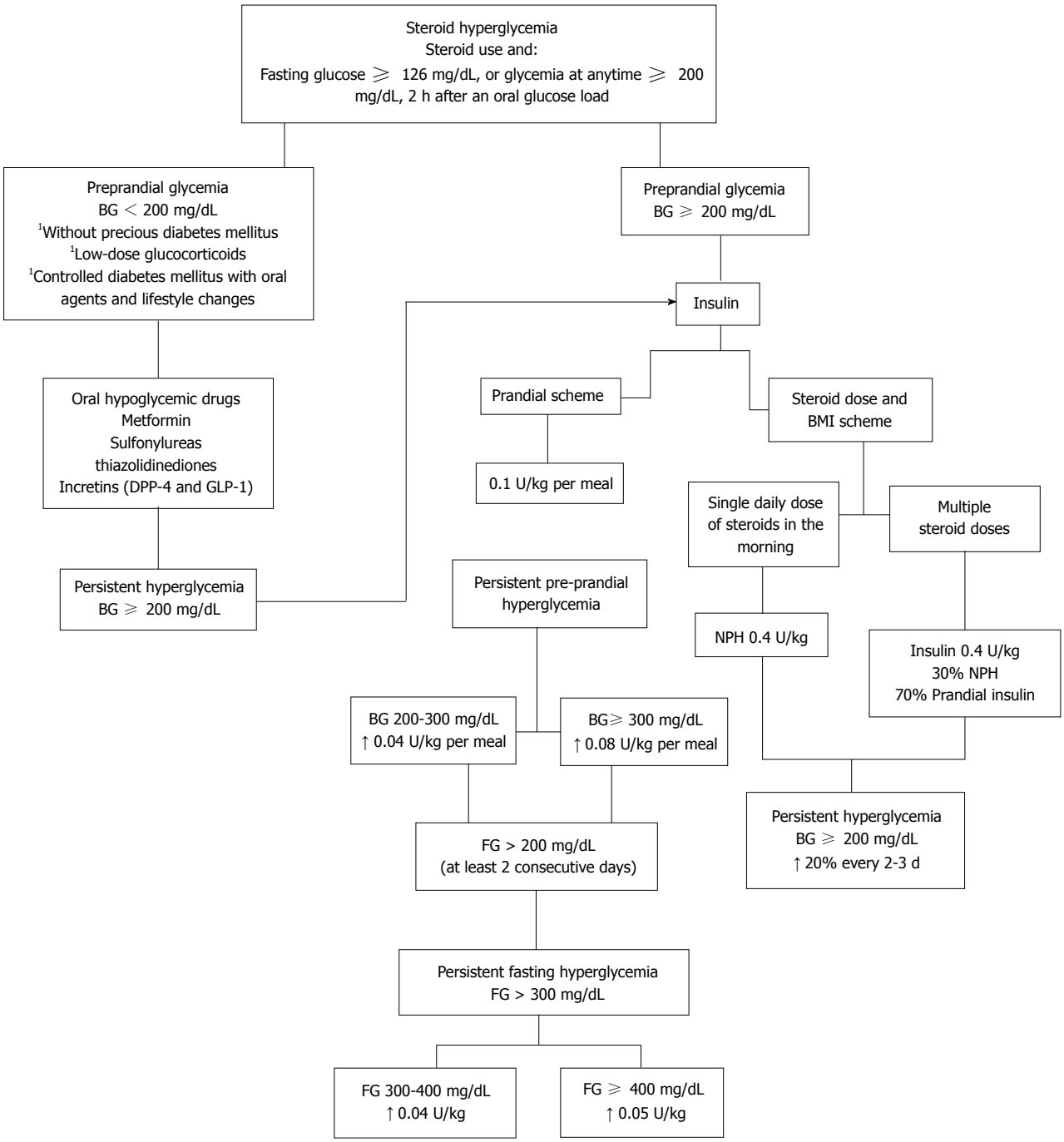

Figure 1 Algorithm for the management of glucocorticoids-induced hyperglycemia. Glargine and other analogues can be recommended in cases of nocturnal hyperglycemia associated with long-acting steroid use. [1]Calculatation rule is: mg/dL × 0.0555 = mmol/L. NPH: Neutral protamine Hadegorn; BG: Blood glucose; FG: Fasting glucose; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; BMI: Body mass index.

with fasting glucose levels below 200 mg/dL, without previous diabetes and given low-dose GCs, therapeutic emphasis should focus on exercise, diet therapy and oral antidiabetic agents[6]. Most available oral hypoglycemic drugs have a slow onset of action and/or a very limited or null titration, giving them little capacity to adapt to major changes in requirements of hypoglycemic action. Furthermore, the action profile of oral hypoglycemic drugs throughout the day does not usually coincide with the pattern of GC induced hyperglycemia[13,25].

Long lasting sulfonylureas were the first drugs used in renal transplant patients, with a therapeutic response of 25%. They have the advantage of being strong inducers of insulin secretion from pancreatic β-cells and secondary by increasing glucose uptake in peripheral tissues[36]. However, due to their narrow therapeutic window, prolonged use increases the risk of hypoglycemia with short-term steroids, especially where single morning doses of steroids are given[14]. In patients where intermediate-acting GCs in two or more daily doses, by long-term preparations such as dexametasone, or by intra-articular GCs are used, long acting sulfonylureas may

be considered as a therapeutic option, always bearing in mind the risk of hypoglycemia in these type of drugs.

Metformin may be a good therapeutic option because of its direct effect on the improvement of insulin sensitivity; however, there are few articles that support its usefulness. On the other hand, many patients who are treated with steroids have significant co-morbidities associated with hypoxia and renal failure, that make the use of metformin contraindicated[13,14].

Thiazolidinediones (TZDs) were used for long-term treatment in patients with steroid-induced hyperglycemia. They act as ligands for PPAR-γ receptors enhancing insulin action in skeletal muscle and adipose tissue, while having little effect on insulin secretion. However, their usefulness is limited by the risk of edema, heart failure, hepatotoxicity and possible cardiovascular effects[37]. They have also been associated with increased risk of fractures, which together with the osteopenic effect of steroids is an important contraindication to their use[1,14].

Selective inhibitors of the dipeptidyl peptidase 4 (DPP-4) enzyme and glucagon-like peptide-1 have shown effectiveness in the control of hyperglycemia since they promote enhanced release of glucose dependent insulin, inhibiting glucagon secretion and enhancing uptake into peripheral tissues, in addition to increasing the speed of gastric emptying, with decreased appetite and calorie intake[13,32,38]. Regarding steroid hyperglycemia, DPP-4 have shown to decrease glycated hemoglobin in up to 24.6% as well as serum glucose levels in 32.6% from baseline[32]. Continuous intravenous infusion of exenatide significantly improves GC-induced hyperglycemia in healthy individuals in association with restoration of initial insulin secretion and decreased glucagon concentrations. Additionally, exenatide has been associated with reduced hypoglycemia and the promotion of weight loss[13]. Despite the benefits observed, their applicability in these patients is still under study. Nevertheless, they can be recommended in patients receiving intermediate-acting corticosteroids in a single morning dose because their immediate onset of action, their predominant effect on postprandial glycemia, and their lack of risk of hypoglycemia related to glucose-dependent effects[25]. A new review has been published with this type of drugs[33].

Glinides allow minimal dose titration and have an immediate onset of action and short duration of effect, which adapts to the hyperglycaemic profile of the corticosteroids and reduces the risk of hypoglycemia in the morning, coinciding with the disappearance of the hyperglycemic action of corticosteroids[25].

Renal sodium-linked glucose transporter 2 inhibitors are new antidiabetic drugs with an insulin-independent mechanism of action. They pose one remarkable advantage compared with already established antidiabetics: increasing urinary glucose excretion without inducing hypoglycaemia, thereby promoting body weight reduction due to loss of approximately 300 kcal per day. Clinical trials showed promising results: enhancing glycaemic control was paralleled by reducing body weight and systolic and diastolic blood pressure. Nevertheless, some safety concerns remain, such as genital mycotic infections, urinary tract infections and cardiovascular risks in vulnerable patients. However in Treatment of steroid hyperglycemia haven't been used[39].

INSULIN

Insulin is the treatment of choice in patients with persistent hyperglycemia ⩾ 200 mg/dL. Several therapeutic schemes have been used, among which the use of prandial insulin has been included, and also based on schemes of steroid dose and the body mass index of the patient[14]. In general, hyperglycemia associated insulin resistance, present at the start of treatment with steroids, generates the need for large doses of insulin in early stages of treatment, which are gradually reduced once glucose levels are controlled[1,12].

PRANDIAL SCHEME

The prandial insulin scheme is based on the observation that even though normal levels of fasting glucose can be present; serum glucose gradually increases throughout the day reaching a maximum concentration after meals, with a gradual reduction at night. This mechanism could be explained by defective postprandial insulin secretion[14].

The scheme is based on the patient's weight, the total calories consumed during the meal, and the establishment of a food pattern. Regular insulin is recommended for people who usually eat snacks between meals and those with delayed gastric emptying; on the other hand, rapid insulin, LysPro and Aspart, are used in people who do not eat snacks between meals and who usually eat a high carbohydrate diet[1,7].

The initial dose is calculated at 0.1 U/kg per meal, and is then modified depending on the glycemic response and the amount of supplementary insulin required to correct the pre-prandial hyperglycemia: 0.04 U/kg per meal with a glucose level between 200-300 mg/dL, 0.08 U/kg per meal if levels are above 300 mg/dL. If the patient continues with pre-prandial corrections the initial insulin dosage should be increased[1].

The use of basal insulin is usually considered when using high doses of steroids are used or in those patients with characteristics of diabetes prior to the start of the steroid. If fasting glucose is above 200 mg/dL on at least two consecutive mornings, NPH should be initiated at 0.1 U/kg before bedtime. If hyperglycemia levels persist > 300 mg/dL despite preprandial corrections, 0.04 U/kg at levels of 300-400 mg/dL and 0.05 U/kg when > 400 mg/dL, can be added. Additionally, glargine can be recommended particularly in cases of nocturnal hypoglycemia[1,34].

Table 2 List of most commonly used drugs in glucocorticoids-induced hyperglycemia and their adverse effects

Drug	Adverse effects
Metformin	Gastrointestinal distress, lactic acidosis, B12 deficiency, contraindicated in renal failure and interactions with other drugs
Insulin	Hypoglycemia, weight gain, cancer-related
Sulfonylureas and Glinides	Hypoglycemia, weight gain, cardiovascular risk
Incretins (DPP-4 inhibitors and GLP-1 agonists)	Gastrointestinal distress, heightened pancreatitis risk, heightened risk of cardiac insufficiency
Thiazolinediones	Weight gain, liquid retention, heightened fracture risk

DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1.

SCHEME BASED ON STEROID DOSE AND THE BMI OF THE PATIENT

In patients who receive a single daily steroid dose, generally in the morning, NPH insulin in the morning is recommended, considering that the peak and duration of action of this insulin is similar to conventional intermediate-steroids (prednisone and prednisolone)[35]. Clore *et al*[14] recommend using a scheme based on weight and steroid dose, using an initial dose of 0.4 U/kg of NPH, with subsequent adjustments depending on the response.

If multiple steroid doses are intended during the day, NPH insulin is usually not enough to maintain glycemic control due to postprandial hyperglycemia, therefore the dose can be divided into 30% basal insulin and 70% nutritional insulin[34]. When using dexamethasone, NPH could be replaced by detemir or glargine due to their pharmacodynamic similarities[14].

Inpatient treatment

In-hospital dose calculation is similar to outpatient doses, with some modifications. If the patient is known to have diabetes with insulin use prior to admission, the dose should be increased 20%. On the other hand, if high doses of steroids are used and the dose must be calculated empirically, the insulin dose will be calculated based on weight 0.7 U/kg per day.

In hospitalized patients receiving high doses of steroids with glucose levels above 400 mg/dL, an insulin infusion pump should be indicated. This indication is particularly important in patients receiving intravenous steroids pulses in which insulin requirements are difficult to predict[2,6].

DOSAGE ADJUSTMENTS

The insulin dose must be adjusted according to capillary glycemias every 2-3 d, with increases and/or decreases around 20%. Additionally, insulin doses should be adjusted based on changes in steroid dose to prevent hyperglycemia and/or hypoglycemia[34]. The percentage of insulin adjustment corresponds to half the percentage in steroid change; for example, if the steroid dose is reduced or increased by 50%, the insulin dose will be reduced or increased 25%, respectively[19,26]. The control goals must be those recommended for patients with DM according to the current criteria: preprandial glycemia 70-130 mg/dL, postprandial glycemia < 180 mg/dL, and HbA1c < 7%[40].

The drugs and their most common adverse effects can be seen in Table 2.

SCIENTIFIC ADVANCES

The understanding of the molecular mechanisms of steroids has allowed the development of compounds that reduce unwanted metabolic effects in comparison to conventional steroids, at the same time maintaining the same anti-inflammatory and immunosuppressive effects. These new drugs are based on the finding of mechanisms by which steroids promote gene transcription (transactivation), differing from those models that inhibit gene transcription (transrepression). Mechanisms related to transrepression are responsible for the anti-inflammatory effects, while those which involve transactivation are associated with known metabolic effects[4,19].

Furthermore, to date various compounds that inhibit the effects of 11β-hydroxysteroid dehydrogenase type 1, which results in improved glucose tolerance, insulin sensitivity, and improvement in lipid profile are under evaluation[4].

CONCLUSION

GCs are drugs that have been widely used in a variety of medical conditions. Despite their medical efficacy, steroid-induced hyperglycemia remains as a common potentially harmful problem that must be considered when using any type a dose of GC. Despite its frequency, little is known about the impact of hyperglycemia associated with steroid use on clinical comorbidity and mortality.

A proper understanding of the mechanisms involved in steroid hyperglycemia is needed, since this will allow early detection and effective treatment in these patients. Appropriate guidelines that establish the recommendations for the diagnosis and treatment of steroid diabetes are needed in order to prevent all de complications associated with the hyperglycemic state. In most cases insulin must be the treatment of choice, especially in cases of serum glucose > 200 mg/dL. Nevertheless an individualized approach must be taken in each patient in order to consider lifestyle modifications and oral hypoglycemic drugs as alternative therapeutic

options.

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